

EP4 RECEPTOR INHIBITORS TO TREAT
RHEUMATOID ARTHRITIS

This application claims priority, under 35 U.S.C. § 119(e), from U.S. provisional application 60/241,825 filed October 19, 2000.

Field of the Invention

The present invention features methods of treating rheumatoid arthritis by administering an agent that inhibits prostaglandin EP4 receptor activity. The invention also includes methods of identifying agents that selectively inhibit prostaglandin EP4 receptor activity *in vivo*.

Background

Prostaglandin E₂ (PGE₂) is a potent modulator involved in the pathogenesis of arthritis. PGE₂ binds to at least four subtypes of PGE receptor, designated EP1, EP2, EP3, and EP4. Molecular studies have revealed that all subtypes are 7-transmembrane spanning receptors that belong to the G-protein coupled receptor superfamily (Robert et al., Am. Soc. Pharm. Exp. Ther. 46: 205-29, 1994). EP1 activation stimulates the release of intracellular calcium via a G protein-mediated mechanism; EP2 and EP4 both activate adenylate cyclase via stimulatory G proteins, but differ in their response to certain ligands; and EP3 inhibits adenylate cyclase via inhibitory G-proteins (Robert et al., *supra*, Negishi et al., Biochimica Biophys. Acta 1259: 109-20, 1995).

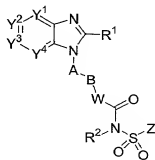
To further elucidate the function of the various EP receptors in PGE₂-mediated signaling, knockout mice strains have been developed in which each of the EP receptors have been targeted for disruption (Stock et al., J. Clin. Invest. 107: 325-31, 2001; Tilley et al., J. Clin. Invest. 103: 1539-45, 1999; Fleming et

al., Am. J. Physiol. 275: F955-61, 1998; Nguyen et al., Nature 390: 78-84, 1997).

Summary of the Invention

The present invention features methods of treating rheumatoid arthritis. In the first aspect, the invention features a method of treating rheumatoid arthritis in a mammal involving administering an agent that inhibits prostaglandin EP4 receptor (EP4) activity. Preferably, the agent is administered in an amount sufficient to reduce interleukin (IL)-6 levels, reduce serum amyloid A (SAA) levels, reduce joint inflammation, reduce joint hyperplasia, reduce joint ankylosis, and/or increase joint mobility in the mammal. Preferably, the mammal is human and/or the agent is EP4 selective.

In another preferred aspect, the agent is an aryl or heteroaryl fused imidazole compound of the following Formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein

Y1, Y2, Y3 and Y4 are independently selected from N, CH or C(L);

R1 is H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₇ cycloalkyl, C₁₋₈ alkoxy, halo-substituted C₁₋₈ alkoxy, C₁₋₈ alkyl-S(O)m-, Q¹-, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(C₁₋₈ alkyl)amino, C₁₋

4alkyl-C(=O)-N(R³)- or C₁₋₄alkyl-S(O)m-N(R³)-, wherein said C₁₋₈ alkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl are optionally substituted with halo, C₁₋₃ alkyl, hydroxy, oxo, C₁₋₄ alkoxy-, C₁₋₄ alkyl-S(O)m-, C₃₋₇ cycloalkyl-, cyano, indanyl, 1,2,3,4-tetrahydronaphtyl, 1,2-dihydronaphtyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹-, Q¹-C(=O)-, Q¹-O-, Q¹-S(O)m-, Q¹-C₁₋₄alkyl-O-, Q¹-C₁₋₄alkyl-S(O)m-, Q¹-C₁₋₄alkyl-C(O)-N(R³)-, Q¹-C₁₋₄alkyl-N(R³)- or C₁₋₄alkyl-C(O)-N(R³)-;

Q¹ is a 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 4 heteroatoms selected from O, N and S, and is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄ alkylthio, nitro, amino, mono- or di-(C₁₋₄alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄alkylC(=O)-, HO(O=)C-, C₁₋₄alkyl-O(O=)C-, R³N(R⁴)C(=O)-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R³C(=O)N(R⁴)- or NH₂(HN=)C-;

A is a 5-6 membered monocyclic aromatic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5-6 membered monocyclic aromatic ring is optionally substituted with up to 3 substituents selected from halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄alkylthio, nitro, amino, mono- or di-(C₁₋₄alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, acetyl, R³N(R⁴)C(=O)-, HO(O=)C-, C₁₋₄alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R³C(=O)N(R⁴)- and NH₂(HN=)C-;

B is halo-substituted C₁₋₆ alkylene, C₃₋₇ cycloalkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, -O-C₁₋₅ alkylene, C₁₋₂ alkylene-O-C₁₋₂ alkylene or C₁₋₆ alkylene optionally substituted with an oxo group or C₁₋₃ alkyl;

W is NH, N-C₁₋₄ alkyl, O, S, N-OR⁵ or a covalent bond;

- 5 R² is H, C₁₋₄ alkyl, OH or C₁₋₄ alkoxy;

Z is a 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl,

- 10 hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄ alkylthio, nitro, amino, mono- or di-(C₁₋₄ alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄alkylC(=O)-, R³C(=O)N(R⁴)-, HO(O=)C-, C₁₋₄alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, NH₂(HN=)C-, Q²-S(O)m-, Q²-O-, Q²-N(R³)- or Q²-;

- 15 L is halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄ alkylthio, nitro, amino, mono- or di-(C₁₋₄ alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄alkylC(=O)-, HO(O=)C-, C₁₋₄alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R³C(=O)N(R⁴)-, NH₂(HN=)C-,

- 20 R³N(R⁴)C(=O)-, R³N(R⁴)S(O)m-, Q²-, Q²-C(=O)-, Q²-O-, Q²-C₁₋₄alkyl-O-, or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;

m is 0, 1 or 2;

R³ and R⁴ are independently selected from H and C₁₋₄ alkyl ;

R⁵ is H, C₁₋₄ alkyl, C₁₋₄ alkyl-(O=)C- or C₁₋₄ alkyl-O-(O=)C- ; and

Q² is a 5-12 membered monocyclic or bicyclic aromatic ring, or a 5-12 membered tricyclic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄ alkylthio, nitro, amino, mono- or di-(C₁₋₄ alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄alkyl-(O=)C-, R³(R⁴)C(=O)N-, HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, C₁₋₄ alkyl-C(=O)NH- or NH₂(HN=)C-.

In another aspect, the invention provides a method of identifying an agent that selectively inhibits EP4 activity *in vivo* involving administering an agent to an animal model of rheumatoid arthritis, wherein the agent is identified as selectively inhibiting EP4 activity or selectively binding EP4, and measuring joint inflammation, joint swelling, joint ankylosis, interleukin (IL)-6, SAA protein, and/or joint mobility, wherein the agent is identified as selectively inhibiting EP4 activity *in vivo* if the agent causes reduced joint inflammation, reduced joint swelling, reduced joint ankylosis, reduced interleukin (IL)-6, reduced SAA protein, and/or increased joint mobility in the animal.

Those skilled in the art will fully understand the terms used herein in the description and the appendant claims to describe the present invention. Nonetheless, unless otherwise provided herein, the following terms are as described immediately below.

By "EP4 receptor activity" or "EP4 activity" is meant an EP4-mediated increase in cAMP levels upon PGE₂ stimulation.

By “an agent that inhibits EP4 activity” or an “EP4 inhibitor” is meant an agent that reduces or attenuates the biological activity of an EP4 receptor. Such agents may include proteins such as anti-EP4 antibodies, nucleic acids, amino acids, peptides carbohydrates, small molecules (organic or inorganic), or any other compound or composition which decreases the activity of an EP4 receptor either by reducing the amount of EP4 receptor present in a cell, or by decreasing the binding or signaling activity of the EP4 receptor.

A “selective” EP4 inhibitor is an agent that inhibits EP4 activity with an IC_{50} at least 10-fold less, preferably, at least 100-fold less than the IC_{50} for inhibition of EP1, EP2, or EP3 activity, as determined by standard methods known in the art.

The term “alkyl”, as used herein, means a straight or branched saturated monovalent hydrocarbon radical including, but not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, neopentyl and the like.

The term “alkenyl”, as used herein, means a hydrocarbon radical having at least one double bond including, but not limited to, ethenyl, propenyl, 1-butenyl, 2-butenyl and the like.

The term “alkynyl”, as used herein, means a hydrocarbon radical having at least one triple bond including, but not limited to, ethynyl, propynyl, 1-butyne, 2-butyne and the like.

The term “halo”, as used herein, refers to F, Cl, Br or I, preferably F or Cl.

The term “cycloalkyl”, as used herein, means a saturated carbocyclic radical including, but not limited to, cyclopropyl, cyclobutyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

The term “alkoxy”, as used herein, means an O-alkyl group wherein “alkyl” is defined above.

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The term "monocyclic aromatic ring", as used herein, means a monocyclic aromatic carbocyclic or heterocyclic ring (and containing 0-4 heteroatoms selected from O, N and S) including, but not limited to, phenyl, pyrazolyl, furyl, thienyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl, thiadiazolyl, 5 pyridyl, pyrimidinyl, pyrrolyl, thiophenyl, pyrazinyl, pyridazinyl, isooxazolyl, isothiazolyl, triazolyl, furazanyl and the like.

The term "bicyclic aromatic ring", as used herein, means a monocyclic or bicyclic aromatic carbocyclic or heterocyclic ring (and containing 0-4 heteroatoms selected from O, N and S) including, but not limited to, naphthyl, 10 benzofuranyl, isobenzofuranyl, benzothiophenyl, indolyl, isoindolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl quinoxalinyl and the like.

The term "alkylene", as used herein, means saturated hydrocarbon (straight chain or branched) wherein a hydrogen atom is removed from each of 15 the terminal carbons such as methylene, ethylene, propylene, butylene, pentylene, hexylene and the like.

The term "cycloalkylene", as used herein, means divalent cycloalkyl groups including, but not limited to, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene and cycloheptylene and the like.

20 The term "alkenylene", as used herein, means a straight or branched hydrocarbon chain spacer radical having at least one double bond including, but not limited to, $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CHCH}-$, $-\text{CH}=\text{CHCH}(\text{CH}_3)-$, and the like.

The term "alkynylene", as used herein, means a straight or branched hydrocarbon chain spacer radical having at least one triple bond including, but 25 not limited to, $-\text{C}=\text{C}-$, $-\text{C}-\text{C}\equiv\text{CCH}_2-$, $-\text{C}\equiv\text{CCH}(\text{CH}_3)-$, and the like.

The term "tricyclic ring", as used herein, means a saturated carbocyclic radical including, but not limited to, adamantyl, tricyclo[5.2.1.0^{2,6}]decane, and the like.

5 The term "two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms", as used herein, means, but not limited to, -O-CH₂-O-, -CH₂-O-CH₂-, -O-CH₂CH₂-, -CH₂CH₂-O-, -O-CH₂CH₂-O-, -CH₂CH₂CH₂-O-, -O-CH₂CH₂CH₂-, -CH₂-O-CH₂CH₂-, -CH₂CH₂-O-CH₂-, and the like.

10 The term "aryl", as used herein, means aromatic radicals including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl and the like.

The term "protecting group", as used herein, means a hydroxy or amino protecting group which is selected from typical hydroxy or amino protecting groups described in Protective Groups in Organic Synthesis edited by T. W. Greene *et al.* (John Wiley & Sons, 1991);

20 The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment" as used herein refers to the act of treating, as "treating" is defined immediately above.

25 Other features and advantages of the invention will be apparent from the following detailed description and from the claims. While the invention is described in connection with specific embodiments, it will be understood that other changes and modifications that may be practiced are also part of this invention and are also within the scope of the appendant claims. This

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application is intended to cover any equivalents, variations, uses, or adaptations of the invention that follow, in general, the principles of the invention, including departures from the present disclosure that come within known or customary practice within the art. Additional guidance with respect to making and using nucleic acids and polypeptides is found in standard textbooks of molecular biology, protein science, and immunology (see, e.g., Davis et al., *Basic Methods in Molecular Biology*, Elsevier Sciences Publishing, Inc., New York, NY, 1986; Hames et al., *Nucleic Acid Hybridization*, IL Press, 1985; *Molecular Cloning*, Sambrook et al., *Current Protocols in Molecular Biology*, Eds. Ausubel et al., John Wiley and Sons; *Current Protocols in Human Genetics*, Eds. Dracopoli et al., John Wiley and Sons; *Current Protocols in Protein Science*, Eds. John E. Coligan et al., John Wiley and Sons; and *Current Protocols in Immunology*, Eds. John E. Coligan et al., John Wiley and Sons). All publications mentioned herein are incorporated by reference in their entireties.

Description of the Figures

Figure 1 is a bar graph showing the severity of arthritic symptoms in wild type (filled bar) and EP receptor knockout (open bar) mice (* $p < 0.05$ by Mann-Whitney).

Figure 2 is a bar graph showing the incidence of arthritic symptoms in wild type (filled bar) and EP receptor knockout (open bar) mice (* $p < 0.05$ by Chi-square test).

Figure 3 is a bar graph showing the number of joints affected by arthritis in wild type (filled bar) and EP receptor knockout (open bar) mice.

Figure 4 is a graph showing the time course for development of arthritic symptoms in WT (filled square) and EP4 receptor knockout (open square) mice (* $p < 0.05$ by Student *t*-test on final day of study only).

Figure 5 is a graph showing the effect of EP4 antagonist Compound A in reducing edema in the ipsilateral paw in rats with adjuvant-induced (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$; significantly different from disease group untreated with compound, as determined by *t*-test or *Mann-Whitney* Rank Sum test).

Figure 6 is a graph showing the effect of EP4 antagonist Compound B in reducing edema in the ipsilateral paw in rats with adjuvant-induced arthritis (* $p < 0.05$, ** $p < 0.01$; significantly different from disease group untreated with compound, as determined by *t*-test or *Mann-Whitney* Rank Sum test).

Figure 7 is a bar graph showing the effects of EP4 antagonist Compound A and Compound B in reducing arthritic scores in the limbs of rats with adjuvant-induced arthritis (* $p < 0.05$, ** $p < 0.01$; significantly different from disease group untreated with compound, as determined by *t*-test or *Mann-Whitney* Rank Sum test).

Detailed Description

The present invention is directed to a method of treating symptoms of rheumatoid arthritis by administering an agent that inhibits EP4 activity. This invention is based upon the discovery that EP4 knockout mice are relatively resistant to developing symptoms of arthritis subsequent to disease induction with administration of an anti-type II collagen antibody (an experimental model for rheumatoid arthritis). The invention also features screening methods to identify agents that inhibit EP4 activity *in vivo* for use, for example, as anti-rheumatoid arthritis therapeutics.

Therapeutic Methods

Agents identified as EP4 inhibitors are administered in a dose sufficient to reduce joint inflammation, joint swelling, joint ankylosis, interleukin (IL)-6, and/or serum amyloid A protein (SAA), and/or sufficient to increase joint mobility. Such therapeutically effective amounts will be determined using routine optimization techniques that are dependent on the particular condition to be treated, the condition of the patient, the route of administration, the formulation, the judgment of the practitioner, and other factors evident to those skilled in the art in light of this disclosure.

An agent that inhibits EP4 activity can be incorporated into a therapeutic composition. Such EP4 inhibitors can include small molecules, nucleic acids, e.g., EP4 antisense nucleic acids, amino acids, peptides, carbohydrates, and anti-EP4 antibodies. Preferably, such agents are combined with a pharmaceutically acceptable delivery vehicle or carrier. Examples of EP4 antibodies include, for example, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric or single chain antibodies, Fab, F(ab')₂, and Fab expression library fragments, scFV molecules, and epitope-binding fragments thereof. An antisense oligonucleotide directed to the EP4 gene or mRNA to inhibit its expression is made according to standard techniques (see, e.g., Agrawal et al. *Methods in Molecular Biology: Protocols for Oligonucleotides and Analogs*, Vol. 20 (1993)).

As used herein, a pharmaceutically acceptable delivery vehicle includes solvents, dispersion media, coatings, antibacterial and antifungal agents, and isotonic and absorption delaying agents that are compatible with pharmaceutical administration. The vehicle may also include other active or inert components, and/or may be targeted to joint tissue by virtue of its composition.

A therapeutic composition is formulated to be compatible with its intended route of administration. Non-limiting examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous,

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oral (e.g., by ingestion or inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions can be made as described in *Remington's Pharmaceutical Sciences*, (18th ed., Gennaro, ed., Mack Publishing Co., Easton, PA, (1990)).

- 5 Therapeutic efficacy of such EP4 inhibitors can be determined in light of this disclosure by standard therapeutic procedures in cell cultures or experimental animals, e.g., for determining the ED₅₀ (the dose therapeutically effective in 50% of the population).

- 10 The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the formulation and the route of administration. For any EP4 inhibitor used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes
- 15 the IC₅₀ as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

- 20 The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a mammal including, but not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the mammal, and other diseases present. Moreover, treatment of a mammal with a therapeutically effective amount of an EP4 inhibitor can include a single treatment or, preferably, can include a series of treatments.

- 25 For anti-EP4 antibodies, the preferred dosage is generally 10 mg/kg to 20 mg/kg body weight. Generally, partially humanized antibodies and fully human antibodies have a longer half-life within the human body than other antibodies.

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Accordingly, lower dosages and less frequent administration are possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration. A method for lipidation of antibodies is described in Cruikshank et al. (J. Acquired Immune Deficiency Syndromes

5 Hum. Retrovirol. 14: 193, 1997).

EP4 inhibitors (e.g., antagonists) that can be administered include the aryl and heteroaryl fused imidazole compounds of Formula I, as further described below, and as described in U.S. provisional application 60/241,825, filed October 19, 2000, and in Akiyoshi et al., a non-provisional application filed on approximately October 10, 2001 and entitled "Aryl or Heteroaryl Fused Imidazole Compounds as Anti-Inflammatory and Analgesic Agents." Other EP4 inhibitors that can be administered include those disclosed in EP 0985663, WO 00/15608, WO 00/03980, WO 98/55468, WO 00/01874, WO 01/42281, WO 01/02855, WO 01/10426, WO 00/16760, WO 00/18744, WO 00/16760, WO 15 00/21532, WO 00/18405, EP 0855389, GB 2330307, and GB 2075503.

EXAMPLE A

1. Reduction of Rheumatoid Arthritis Symptoms in EP4 Receptor Knockout Mice

Methods

Generation of genetically modified mice.

EP1 receptor knockout (EP1-KO), EP2-KO, EP3-KO, and EP4-KO mice were generated as previously described (Stock et al., J. Clin. Invest. 107: 325-31, 2001;

25 Tilley et al., J. Clin. Invest. 103: 1539-45, 1999; Fleming et al., Am. J. Physiol. 275: F955-61, 1998; Nguyen et al., Nature 390: 78-84, 1997, respectively). EP1-KO mice were maintained on a DBA1/lacJ genetic background. EP2-KO and EP4-KO mice were maintained on a 129xDBA/2xC57/Bl6 genetic background. EP2 and EP4 littermate wild type mice (WT) were used as controls. EP3-KO animals were

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maintained on a 129Sv/Ev genetic background. All experiments were performed on 8-10 week old mice (approximate weight: 20g).

Induction and visual assessment of rheumatoid arthritis.

Arthritis was induced in mice using a monoclonal antibody directed against Type II collagen (mAb treatment). The mAb treatment involved an intraperitoneal (i.p.) injection (400 μ l, 10 mg/ml) of a monoclonal antibody cocktail (Chemicon International Inc., Temecula, CA) in the mice on Day 0. After 24 hours, mice were injected i.p. with lipopolysaccharide (LPS) (100 μ l, 0.25 mg/ml) (Chemicon International Inc.) For 10 days following the antibody injection, arthritis was assessed by the degree of swelling, redness, and ankylosis of the joints. All visual factors were combined into a score of 0-3 per paw and summed for a total score of 0-12 for each animal.

Histological assessment.

On Day 10 following antibody injection (Day 10), mice were euthanized by CO₂ asphyxiation, and tissue samples were subjected to a comprehensive histological assessment that included evaluations of cartilage structure, cellularity, Safranin-O staining for acid mucopolysaccharides, and synovial inflammation and hyperplasia to develop Modified Mankin scores (Mankin, et al., J. Bone and Joint Surgery 53: 523-537, 1971). Originally developed to quantify changes in articular cartilage in humans with osteoarthritis, the Mankin scale was modified for rodents to reflect rodent size and to include synovial inflammation. The scores were based upon a scale of 0-4 (with 4 designated for the most severe form of arthritic symptoms) graded on a relative severity scale developed for the spectrum of lesions observed in these studies.

9A4-immunohistochemical staining was conducted as previously described (Otterness et al., Matrix Biology 18: 331-41, 1999). The scores were

graded as follows: score = 0, normal cartilage; score = 4, diffuse staining reflecting severe bone and cartilage damage.

Serum collection.

Following euthanization, mice were bled by cardiac puncture. Using a gentle vacuum, blood was collected in Microtainer® serum separator tubes (Becton Dickinson, Franklin Lakes, NJ) and spun at 1000xg for 10 min. at 4°C. The serum fraction was collected and stored at -20°C until assayed for PGE₂ (Cayman Chemical, Ann Arbor, MI), IL-6 (R&D Systems, Inc., Minneapolis, MN), and serum amyloid A (SAA) (Biosource International, Camarillo, CA) levels.

Exudate collection.

Peritoneal macrophages were collected by removing the skin from the abdomen of Day 10 euthanized mice, and injecting 8 ml of lavage fluid (500 ml Hanks's Balanced Salt Solution, 1 ml 1% EDTA) into the peritoneal cavity. The solution was collected from the peritoneal cavity and placed in 50 ml conical polystyrene tubes on ice. The samples were spun for 10 min. at 300xg at room temperature. Lavage fluid (containing peritoneal exudates) was isolated and stored at -20°C until assayed. Interleukin (IL)-6 and PGE₂ levels were measured as described previously. Total protein content was determined by BCA assay (Pierce Chemical, Rockford, IL).

Peritoneal macrophage culture.

After the collection of peritoneal macrophages as previously described, the cells were washed twice with lavage solution, and twice with modified DMEM (DMEM, 1% fetal bovine serum, 1% penicillin/streptomycin). The cells were resuspended in 10 ml modified DMEM and the cell concentration was diluted to 10⁶/ml in modified DMEM. Cells were plated in 96-well plates (100 µl/well), and incubated at 37°C, 95% O₂, 5% CO₂ for 1-2 hours. After the

incubation, the supernatant was removed from the plates by inversion in a sterile tissue culture hood. Each well was washed twice with PBS, and the macrophages were then incubated for 18 hours at 37°C, 95% O₂, 5% CO₂.

Supernatants from each well were then carefully removed and placed at -20°C

- 5 until analysis for IL-6 as previously described.

β -hexaminidase levels were measured in cell lysates from the remaining macrophages and used to normalize for variability in cell numbers. After

collecting the supernatants, the peritoneal macrophages were lysed by adding 200 μ l/well of lysis buffer (25 mM HEPES, pH 7, 0.5% Triton X-100, 250 mM

- 10 NaCl and proteinase inhibitors (1 μ g/ μ l pepstatin, 1 μ g/ μ l leupeptin, 0.1 mM phenylmethylsulfonyl fluoride, all available from Sigma Chemical Co., St. Louis, MO). Plates were incubated on ice for 30 min., and lysates were collected. The lysate sample (10 μ l) was combined with 50 μ l substrate (50 mM sodium citrate, pH 4, 0.2% Triton X-100, 2 mM p-nitrophenyl N-acetyl-beta-D-
15 glucosamine (Sigma Chemical Co.) and incubated at 37°C for 60 min. Reactions were stopped with 100 μ l carbonate stop solution (0.11 M Na₂CO₃, 0.09 M NaHCO₃, final pH about 10) and well absorbance was read at 415 nm.

Quantitative mRNA determination.

Livers and peritoneal macrophages were harvested from Day 10

- 20 euthanized mice and snap frozen on dry ice. Total RNA was isolated using Maxiprep columns (Qiagen, Valencia, CA) and stored at -80°C until assayed. Absorbance at 260 and 280 nm were determined to estimate RNA levels and purity. All samples had an A₂₆₀ to A₂₈₀ ratio greater or equal to 1.7. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and IL-1 mRNA levels
25 were determined by enzyme immunoassay (Quantikine®, R&D systems). GAPDH levels were used to normalize IL-1 mRNA levels.

EP4 mRNA was measured in WT and EP4-KO liver and peritoneal macrophages by reverse transcription polymerase chain reaction (RT-PCR), using the sense and antisense primers ggctcattctactcgcacacctc (SEQ ID NO: 1) and tcccaataacctatccaccaacag (SEQ ID NO: 2), respectively (Suzawa, et al. 5 Endocrinology 141: 1554-1559, 2000). Cycling conditions were: 94°C for 2 min.; 30 cycles at 94°C for 30 seconds, 65°C for 30 seconds, and 75°C for 60 seconds; and 72°C for 2 min.

Results

Visual scores of arthritis.

10 Each strain of knockout mouse and its corresponding WT genetic control was tested for the development of rheumatoid arthritis following mAb treatment. The signs of arthritis in WT mice appeared 3-4 days following mAb treatment and reached their maximum by Day 10. Therefore, the final assessment of arthritis development was performed in all mouse lines on Day 10. All four wild 15 type genetic controls developed comparable scores for arthritis on Day 10, indicating that the differences in genetic background did not lead to detectable differences in disease severity and/or incidence (Figures 1 and 2, respectively).

EP1-KO, EP2-KO, and EP3-KO mAb-treated mice did not display any significant differences from their appropriate WT control in the incidence or 20 severity of the arthritic symptoms. By contrast, EP4-KO mAb treated mice demonstrated a significant reduction in the severity of the symptoms (Figure 1), in the number of mice that displayed arthritic symptoms (Figure 2), and in the number of joints affected (Figure 3) as compared to mAb-treated WT controls. The differences in arthritis severity were evident throughout the time course of 25 disease development (Figure 4).

Histology.

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MAb-treated EP4-KO mice also displayed a significantly improved histology as compared to their mAb-treated WT controls as shown by Modified Mankin score (Table 1). MAb-treated WT mice often developed a severe form of arthritis with the formation of multiple erosions on the cartilage surface, cellular hyperplasia, loss of proteoglycan, and pannus formation. The articular cartilage of the mAb-treated EP4-KO mice were significantly protected from such damage (Table 1). 9A4 immunohistochemical staining, which correlates with type II collagen breakdown, was also increased in the mAb-treated WT mice as compared to mAb-treated EP4-KO mice, indicating an increase in cartilage integrity in the mAb-treated EP4-KO mice (Table 1).

Table 1

	mAb-treated WT mean ± s.e.m. (n)	mAb-treated EP4-KO mean ± s.e.m. (n)
Mankin score	11.1±0.4 (14)	4.7±0.7 (15)
9A4 score	1.8±0.5 (14)	0.2±0.1 (15)

Clinical biomarkers of arthritis-associated inflammation.

Clinical biomarkers of arthritis were determined in the serum and peritoneal exudates of mAb-treated and non-treated EP4-KO and WT mice. SAA levels were significantly elevated in the WT mAb-treated group as compared to the WT non-treated controls. By contrast, EP4-KO mice did not display any increases in serum levels of this marker of inflammation as a result of mAb treatment (Table 2).

Serum levels of IL-6 following mAb treatment were increased in both the mAb treated EP4-KO and WT groups, although the WT group increased to a greater extent (Table 2). Peritoneal exudate levels of IL-6 and PGE2 followed the same pattern (Table 2). These levels in mAb treated EP4-KO mice were

increased compared to the non-treated EP4-KO mice, but significantly lower as compared to mAb treated WT mice.

Table 2

	Non-treated		MAb-treated	
	WT	EP4-KO	WT	EP4-KO
collagen II mAb (U/ μ l)	30 \pm 1(6)	37 \pm 3(6)	*2226 \pm 276(8)	*2790 \pm 69(8)
SAA (μ g/ml)	552 \pm 138(6)	209 \pm 72(6)	*3952 \pm 1555(8)	293 \pm 57(8)
serum IL-6 (pg/ml)	8 \pm 5(6)	8 \pm 5(6)	*159 \pm 69(8)	*61 \pm 25(8)
exudate IL-6 (pg/ml)	1 \pm 1(6)	1 \pm 1(6)	*19 \pm 6(6)	6 \pm 3(6)
exudate PGE ₂ (pg/ml)	803 \pm 608(6)	182 \pm 48(6)	*3346 \pm 561(8)	1541 \pm 415(8)

* p<0.05 by 2-way ANOVA and Bonferroni post test

In view of the significant differences in levels of inflammatory mediators detected in peritoneal exudates between mAb treated WT and EP4-KO mice, the properties of peritoneal macrophages isolated from these animals were further characterized for IL-6 levels.

Under baseline conditions, WT macrophages released significantly more IL-6 than EP4-KO macrophages (8.6 ± 0.1 ng/ml/ β -hexaminidase OD (n=3) and 5.4 ± 0.2 ng/ml/ β -hexaminidase OD (n=3), respectively, p<0.05). The integrity of the signaling properties was tested by incubating WT and EP4-KO cells with 1 μ g/ml LPS. Under these conditions, there were no detectable differences in IL-6 levels between WT and EP4-KO macrophages (36.4 ± 6.7 ng/ml/ β -hexaminidase OD (n=3) and 34.9 ± 8.2 ng/ml/ β -hexaminidase OD (n=3), respectively).

mRNA in liver and peritoneal macrophages.

The liver and peritoneal macrophages are involved in the synthesis and release of inflammatory mediators. There were no detectable differences in IL-1 mRNA levels (IL-1 RNA (pg)/ GAPDH RNA (pg)) between non-treated WT and EP4-KO mice (36.4 ± 6.7 (n=4), and 34.9 ± 8.2 (n=4), respectively). However, following mAb treatment, levels were significantly reduced in the EP4-KO mice (57.4 ± 4.4 (n=4) for WT, 20.6 ± 2.7 (n=4) for EP4-KO, $p < 0.05$ by 2-way ANOVA).

Measures of EP4 mRNA confirmed EP4 expression in WT liver and peritoneal macrophages. As expected, no EP4 mRNA was detected in the EP4-KO samples.

2. Reduction of Rheumatoid Arthritis Symptoms In EP4 Antagonist-Treated Rats

Methods

15 Induction of adjuvant arthritis.

Arthritis was induced in male, Sprague-Dawley rats (115-145g, Japan SLC Inc., Shizuoka, Japan) on Day 0 by an injection of $300 \mu\text{g}$ of *M. Tuberculosis* H37 RA (Difco Laboratories Inc., Detroit, MI) in $100 \mu\text{l}$ of liquid paraffin (Wako Pure Chemical Industries, Ltd., Osaka, Japan) into the right hind footpad (Neuroscience 78: 843-850, 1997) on Day 0.

Compound treatment.

EP4 antagonists included within Formula I as described above (compound A and B, 60 mg/kg , bid), piroxicam (Feldene®, 3 mg/kg , qd), rofecoxib (Vioxx®, 1.5 mg/kg , bid), and control vehicle were each suspended in 0.1% methylcellulose (MC) and perorally administered separately in five groups of rats from day 0 to day 14 in a volume of 1 ml per 100 g body weight.

Evaluation.

Hindpaw volume was measured by an hydroplethysmometer (Ugo Basile, Comerio, Italy) on Day 0, immediately before adjuvant injection, and on Days 1, 4, 7, 11 and 14 after injection. Paw swelling (%) was calculated as follows

5 (Agents and Actions 34: 63-65, 1991):

swelling (%) = {Day X volume (ml) – Day 0 volume (ml)} / Day 0 volume (ml) x 100.

On Day 14, the arthritic score of each paw was evaluated as described below. The total arthritic score for each animal was the sum of the score for all
10 four limbs (Agents and Actions 27: 356-358, 1989). A score of 0 was used for limbs with no arthritic symptoms; a score of 1 was used for limbs with redness and swelling in two or less digits or locally in part of the foot pad; a score of 2 was used for limbs with redness and swelling of more than two digits, or in two or less digits and locally in part of the foot pad, or in the whole foot pad; a score
15 of 3 was used for limbs with redness and swelling in more than two digits and locally in part of the foot pad, or in less than two digits and the whole foot pad; a score of 4 was used for limbs with redness and swelling in more than two digits and in the whole foot pad.

Statistical analysis.

20 Data are expressed as mean±SEM (n=8) and statistical significance was evaluated by *t*-test or *Mann-Whitney* Rank Sum test (**p*<0.05, ***p*<0.01, ****p*<0.005 significantly different from disease group untreated with compound).

Results

25 *Paw edema of adjuvant arthritis.*

There was a rapid and time-dependent increase in paw volume in the ipsilateral paw following injection of adjuvant. From Day 9 to Day 12, the

edema symptoms of arthritis had spread to joints in the whole body, not just the joints at the site of injection. Groups treated with EP4 antagonist compound A and compound B demonstrated significantly suppressed edema formation in the ipsilateral paws during the entire experimental period (Figure 5 and Figure 6).

- 5 On day 14, compound A and compound B inhibited paw edema by 45.6 and 47.1%, respectively (Table 3). These effects were comparable to that of the piroxicam treated group. The rofecoxib-treated group showed a weaker activity.

Table 3

	% inhibition ipsilateral paw	% inhibition contralateral paw
Compound A	45.6**	74.9
Compound B	47.1**	73.0
Piroxicam	50.8**	96.2*
Rofecoxib	37.1*	25.6

10 *Arthritic score*

As shown in Figure 7, the groups treated with EP4 antagonist compound A and compound B demonstrated significantly reduced arthritics score on day 14, reduced by 34.1% and 29.6%, respectively (Table 4).

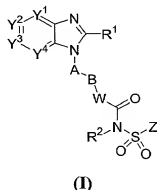
Table 4

	% inhibition
Compound A	34.1*
Compound B	29.6*
Piroxicam	26.7**
Rofecoxib	18.5**

In summary, these results demonstrate that treatment with an EP4 antagonist produces an anti-inflammatory effect in chronic inflammatory diseases such as rheumatoid arthritis and inhibits the formation of arthritis.

5 **EP4 Antagonists: Aryl and Heteroaryl Fused Imidazole Compounds of Formula I**

Aryl and heteroaryl fused imidazole compounds of Formula I have the following formula:



or the pharmaceutically acceptable salts thereof.

In the compounds of Formula I,

- 15 Y¹, Y², Y³, and Y⁴ are preferably independently selected from N, CH and C(L);
 L is halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, mono-
 or di-(C₁₋₄ alkyl)amino, halo-substituted C₁₋₄ alkoxy, cyano, HO-C₁₋₄ alkyl,
 C₁₋₄ alkoxy-C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylC(=O)-,
 HO(O=C)-, C₁₋₄ alkyl-O(O=C)-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl,
 20 R³C(=O)N(R⁴)-, R³N(R⁴)C(=O)-, R³N(R⁴)S(O)_m-, Q²-, Q²-C(=O)-, Q²-O-,
 Q²-C₁₋₄alkyl-O-, or two adjacent L groups are optionally joined together to

form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;

m is 0 or 2;

R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and

- 5 Q² is a 5-12 membered monocyclic or bicyclic aromatic ring, or a 8-12 membered tricyclic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄ alkylthio, mono- or di-(C₁₋₄ alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkyl-(O=)C-, R³(R⁴)C(=O)N-, HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl or C₁₋₄ alkyl-C(=O)NH-, more preferably Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C(L);
 - 15 L is halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, mono- or di-(C₁₋₄ alkyl)amino, halo-substituted C₁₋₄ alkoxy, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylC(=O)-, HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R³C(=O)N(R⁴)-, R³N(R⁴)C(=O)-, R³N(R⁴)S(O)m-, Q²-, Q²-C(=O)-, Q²-O-, Q²-C₁₋₄alkyl-O-,
 - 20 or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;
- m is 0 or 2;
- R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and

Q² is a 5 or 6 membered monocyclic aromatic ring, or a 8-12 membered tricyclic ring containing up to 3 heteroatoms selected from N and S, wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo, more preferably Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C(L);

5 m is 0 or 2;

R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and

Q² is 5 or 6 membered monocyclic aromatic ring or a 8-12 membered tricyclic ring optionally containing 1 sulfur atom wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo, more preferably

10 Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C(L);

L is halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, cyano, HO-C₁₋₄ alkyl, acetyl, R³N(R⁴)C(=O)-, R³N(R⁴)S(O)m-, Q²-, Q²-C(=O)-, Q²-O-, Q²-C₁₋₄alkyl-O-, or two adjacent L groups are joined together to form a methylenedioxy group;

15 R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and

Q² is 5 or 6 membered monocyclic aromatic ring system, more preferably Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C-L;

L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, -C(=O)NH₂, trifluoromethyloxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy group, more preferably Y¹, Y², Y³ and Y⁴ are selected from the group consisting of

a) Y¹ and Y³ are C(L), Y² is CH and Y⁴ is N;

b) Y¹ is CH, Y² and Y³ are C(L) and Y⁴ is N;

- c) Y¹, Y² and Y³ are C(L) and Y⁴ is N;
- d) Y¹ and Y³ are C(L), Y² is N and Y⁴ is CH;
- e) Y¹ is C(L) and Y², Y³ and Y⁴ are CH;
- f) Y¹, Y³ and Y⁴ are CH, and Y² is C(L);
- 5 g) Y¹, Y² and Y³ are CH, and Y⁴ is C(L);
- h) Y¹ and Y² are C(L), and Y³ and Y⁴ are CH;
- i) Y¹ and Y³ are C(L), and Y² and Y⁴ are CH;
- j) Y¹ and Y⁴ are CH, and Y² and Y³ are C(L);
- k) Y¹ and Y² are CH, Y³ is C(L) and Y⁴ is N;
- 10 l) Y¹ and Y³ are CH, Y² is C(L) and Y⁴ is N;
- m) Y¹, Y², Y³ and Y⁴ are CH;
- n) Y¹ and Y² are C(L), Y³ is CH and Y⁴ is N;
- o) Y¹, Y² and Y⁴ are CH, and Y³ is C(L);
- p) Y¹ and Y² are C(L), Y³ is N and Y⁴ is CH;
- 15 q) Y¹ and Y³ are C(L), and Y² and Y⁴ are N;
- r) Y¹ is C(L), Y² and Y³ are CH, and Y⁴ is N;
- s) Y² is C(L), Y¹ and Y³ are CH, and Y⁴ is N; and
- t) Y¹, Y² and Y³ are C(L), and Y⁴ is CH
- L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, –
- 20 C(=O)NH₂, trifluoromethyloxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy group, most preferably Y¹, Y², Y³ and Y⁴ are selected from the group consisting of
- a) Y¹ and Y³ are C(L), Y² is CH and Y⁴ is N;

- b) Y¹ is CH, Y² and Y³ are C(L) and Y⁴ is N;
 c) Y¹, Y² and Y³ are C(L) and Y⁴ is N;
 d) Y¹ and Y³ are C(L), Y² is N and Y⁴ is CH;
 e) Y¹ is C(L) and Y², Y³ and Y⁴ are CH;
 5 f) Y¹, Y³ and Y⁴ are CH, and Y² is C(L);
 g) Y¹, Y² and Y³ are CH, and Y⁴ is C(L);
 h) Y¹ and Y² are C(L), and Y³ and Y⁴ are CH;
 i) Y¹ and Y³ are C(L), and Y² and Y⁴ are CH;
 j) Y¹ and Y⁴ are CH, and Y² and Y³ are C(L); and
 10 k) Y¹, Y² and Y³ are C(L), and Y⁴ is CH
 L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, –
 C(=O)NH₂, trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methyl-
 ethyl, or two adjacent L groups are joined together to form a methylenedioxy
 group.
 15 In the compounds of Formula I,
 R¹ is preferably H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₇ cycloalkyl, C₁₋₈
 alkoxy, halo-substituted C₁₋₈ alkoxy, C₁₋₈ alkyl-S(O)m-, Q¹-, pyrrolidinyl,
 piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(C₁₋₈ alkyl)amino,
 C₁₋₄alkyl-C(=O)-N(R³)- or C₁₋₄alkyl-S(O)m-N(R³)-, wherein said C₁₋₈ alkyl,
 20 C₂₋₈ alkenyl and C₂₋₈ alkynyl are optionally substituted with halo, C₁₋₃ alkyl,
 hydroxy, oxo, C₁₋₄ alkoxy-, C₁₋₄ alkyl-S(O)m-, C₃₋₇ cycloalkyl-, cyano,
 indanyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, pyrrolidinyl, piperidyl,
 oxopyrrolidinyl, oxopiperidyl, Q¹-, Q¹-C(=O)-, Q¹-O-, Q¹-S(O)m-, Q¹-C₁₋₄

alkyl-O-, Q¹-C₁₋₄ alkyl-S(O)m-, Q¹-C₁₋₄alkyl-C(O)-N(R³)-, Q¹-C₁₋₄alkyl-N(R³)- or C₁₋₄alkyl-C(O)-N(R³)-;

Q¹ is a 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 4 heteroatoms selected from O, N and S, and is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄ alkylthio, nitro, amino, mono- or di-(C₁₋₄ alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylC(=O)-, HO(O=)C-, C₁₋₄ alkyl-O(O)C-, R³N(R⁴)C(=O)-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R³C(=O)N(R⁴)- or NH₂(HN=)C-;

m is 0 or 2; and

R³ is H or C₁₋₄ alkyl, more preferably R¹ is H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₇ cycloalkyl, Q¹-, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(C₁₋₈ alkyl)amino, wherein said C₁₋₈ alkyl is optionally substituted with halo, C¹⁻³ alkyl, hydroxy, oxo, C₁₋₄ alkoxy-, C₁₋₄ alkyl-S(O)m-, C₃₋₇ cycloalkyl-, cyano, indanyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹-, Q¹-C(O)-, Q¹-O-, Q¹-S- or Q¹-C₁₋₄ alkyl-O-, or C₁₋₄alkyl-C(O)-N(R³)-;

Q¹ is a 5-12 membered monocyclic aromatic ring optionally containing up to 4 heteroatoms selected from N and S, and is optionally substituted with halo, C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl and C₁₋₄ alkylC(=O)-; and

m is 0 or 2, more preferably R¹ is H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₇ cycloalkyl, Q¹-, or mono- or di-(C₁₋₈ alkyl)amino wherein said C₁₋₈ alkyl

is optionally substituted with halo, C₁₋₃ alkyl, hydroxy, oxo, C₁₋₄ alkoxy-, C₁₋₄ alkyl-S(O)m-, C₃₋₇ cycloalkyl-, cyano, indanyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹-, Q¹-C(=O)-, Q¹-O-, Q¹-S-, Q¹-C₁₋₄ alkyl-O-, or C₁₋₄alkyl-C(O)-N(H)-;

- 5 Q¹ is a 5 or 6 membered monocyclic aromatic ring optionally containing up to 4 heteroatoms selected from N and S; and

m is 0 or 2, more preferably R¹ is C₁₋₅ alkyl, C₃₋₇ cycloalkyl, or Q¹-, mono- or di-(C₁₋₈ alkyl)amino wherein said C₁₋₅ alkyl is optionally substituted with C₁₋₃ alkyl, hydroxy, oxo, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹-,
10 or C₁₋₄alkyl-C(O)-N(H)-; and

Q¹ is 5-12 membered monocyclic aromatic ring system optionally containing up to 2 heteroatoms selected from N and S, more preferably R¹ is C₁₋₅ alkyl, mono- or di-(C₁₋₈ alkyl)amino, pyrrolidinyl, or pyridyl optionally substituted with C₁₋₃ alkyl, hydroxy, oxo, 5 or 6 membered monocyclic aromatic ring,
15 wherein said 5 or 6 membered monocyclic aromatic ring is containing 1 or 2 heteroatoms selected from N and S, or C₁₋₄alkyl-C(O)-N(H)-, most preferably R¹ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl, thiazolethyl methylamino, dimethylamino, pyrrolidinyl, pyridyl, or 1-acetylamino-1-methylethyl,

- 20 In the compounds of Formula I,

R² is preferably H or C₁₋₄ alkyl, most preferably H.

In the compounds of Formula I,

A is preferably a 5-6 membered monocyclic aromatic ring optionally containing up to 2 heteroatoms selected from O, N, and S, wherein said 5-6 membered

monocyclic aromatic ring is optionally substituted with up to 2 substituents selected from halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy and halo-substituted C₁₋₄ alkoxy, more preferably 5-6 membered monocyclic aromatic ring optionally substituted with halo, C₁₋₄ alkyl or C₁₋₄ alkoxy, more preferably 5-6 membered monocyclic aromatic ring system optionally substituted with halo or C₁₋₄ alkyl, more preferably 5-6 membered monocyclic aromatic ring system, most preferably phenyl or pyridyl.

In the compounds of Formula I,

B is preferably C₃₋₇ cycloalkylene or C₁₋₆ alkylene optionally substituted with an oxo group or C₁₋₃ alkyl, more preferably C₁₋₃ alkylene optionally substituted with C₁₋₃ alkyl, more preferably C₁₋₂ alkylene optionally substituted with methyl, most preferably ethylene or propylene.

In the compounds of Formula I,

W is preferably NH, N-C₁₋₄ alkyl, O or N-OH, more preferably NH, N-C₁₋₂ alkyl or O, most preferably NH, N-CH₃ or O.

In the compounds of Formula I,

Z is preferably a 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from, N, O, and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, hydroxy, C₁₋₄ alkoxy, nitro, amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylC(=O)-, R³C(=O)N(R⁴)-, HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₁₋₄ alkyl-C(=O)NH-, Q²-S(O)m-, Q²-O-, Q²-N(R³)- or Q²-;

m is 0 or 2;

R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and

Q² is a 5-12 membered monocyclic or bicyclic aromatic ring, or a 8-12 membered tricyclic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is

- 5 optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄ alkylthio, mono- or di-(C₁₋₄ alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkyl-(O=)C-, R³(R⁴)C(=O)N-, HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino,
- 10 C₃₋₇ cycloalkyl or C₁₋₄ alkyl-C(=O)NH-, more preferably Z is 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkoxy, nitro, amino, cyano, R³C(=O)N(R⁴)-,
- 15 C₁₋₄ alkyl-O(O=)C-, Q²-S(O)_m-, Q²-O-, Q²-N(R³)- or Q²-;
- m is 0 or 2;

R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and

Q² is a 5 or 6 membered monocyclic aromatic ring, or a 8-12 membered tricyclic ring containing up to 3 heteroatoms selected from N and S, wherein said 5 or 6

- 20 membered monocyclic aromatic ring is optionally substituted with halo, more preferably Z is 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkoxy, nitro,

amino, cyano, $R^3C(=O)N(R^4)-$, $C_{1-4} \text{ alkyl-O(O)=C-}$, $Q^2-S(O)m-$, Q^2-O- , $Q^2-N(R^3)-$ or Q^2- ;
m is 0 or 2;

R^3 and R^4 are independently selected from H and C_{1-4} alkyl; and

- 5 Q^2 is 5 or 6 membered monocyclic aromatic ring or a 8-12 membered tricyclic ring optionally containing 1 sulfur atom wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo, more preferably Z is 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5-12 membered
- 10 monocyclic aromatic ring is optionally substituted with halo, C_{1-4} alkyl, nitro, $R^3C(=O)N(R^4)-$ or Q^2- ;
 R^3 and R^4 are independently selected from H and C_{1-4} alkyl; and
- Q^2 is 5 or 6 membered monocyclic aromatic ring system, more preferably Z is 5-10 membered monocyclic or bicyclic aromatic ring optionally containing up to 3
- 15 heteroatoms selected from N and S, wherein said 5-10 membered monocyclic aromatic ring is optionally substituted with chloro, bromo, methyl, nitro, $CH_3C(=O)NH-$, $tBuC(=O)NH-$ or phenyl, most preferably Z is phenyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, naphthyl or benzothienyl, said phenyl, pyrazolyl, thiazolyl, thiadiazolyl and thienyl being optionally substituted with
- 20 one to three substituents independently selected from chloro, bromo, methyl, acetylamino, pivaloylamino, nitro and phenyl.

A preferred group of compounds of Formula I includes compounds wherein

Y^1 , Y^2 , Y^3 , and Y^4 are independently selected from N, CH and C(L);

R¹ is H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₇ cycloalkyl, C₁₋₈ alkoxy, halo-substituted C₁₋₈ alkoxy, C₁₋₈ alkyl-S(O)m-, Q¹-, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(C₁₋₈ alkyl)amino, C₁₋₄alkyl-C(=O)-N(R³)- or C₁₋₄alkyl-S(O)m-N(R³)-, wherein said C₁₋₈ alkyl, C₂₋

- 5 g alkenyl and C₂₋₈ alkynyl are optionally substituted with halo, C₁₋₃ alkyl, hydroxy, oxo, C₁₋₄ alkoxy-, C₁₋₄ alkyl-S(O)m-, C₃₋₇ cycloalkyl-, cyano, indanyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹-, Q¹-C(=O)-, Q¹-O-, Q¹-S(O)m-, Q¹-C₁₋₄ alkyl-O-, Q¹-C₁₋₄ alkyl-S(O)m-, Q¹-C₁₋₄alkyl-C(=O)-N(R³)-, or C₁₋₄alkyl-C(=O)-N(R³)-;

- 10 Q¹ is a 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 4 heteroatoms selected from O, N and S, and is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄ alkylthio, nitro, amino, mono- or di-
 15 (C₁₋₄ alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylC(=O)-, HO(O=)C-, C₁₋₄ alkyl-O(O)C-, R³N(R⁴)C(=O)-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R³C(=O)N(R⁴)- or NH₂(HN=)C-;

- A is a 5-6 membered monocyclic aromatic ring optionally containing up to 2
 20 heteroatoms selected from O, N, and S, wherein said 5-6 membered monocyclic aromatic ring is optionally substituted with up to 2 substituents selected from halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy and halo-substituted C₁₋₄ alkoxy;

B is C₃₋₇ cycloalkylene or C₁₋₆ alkylene optionally substituted with an oxo group or C₁₋₃ alkyl;

W is NH, N-C₁₋₄ alkyl, O or N-OH;

R² is H or C₁₋₄ alkyl;

- 5 Z is a 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, hydroxy, C₁₋₄ alkoxy, nitro, amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylC(=O)-, R³C(=O)N(R⁴)-, HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₁₋₄ alkyl-C(=O)NH-, Q²-S(O)m-, Q²-O-, Q²-N(R³)- or Q²-;
- 10 L is halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, mono- or di-(C₁₋₄ alkyl)amino, halo-substituted C₁₋₄ alkoxy, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylC(=O)-, HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R³C(=O)N(R⁴)-, R³N(R⁴)C(=O)-, R³N(R⁴)S(O)m-, Q²-, Q²-C(=O)-, Q²-O-, Q²-C₁₋₄alkyl-O-, or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;
- 20 m is 0 or 2;
- R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and
- Q² is a 5-12 membered monocyclic or bicyclic aromatic ring, or a 8-12 membered tricyclic ring optionally containing up to 3 heteroatoms selected from

O, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, C₁₋₄ alkylthio, mono- or di-(C₁₋₄ alkyl)amino, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkoxy-
 5 C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkyl-(O=)C-,
 R³(R⁴)C(=O)N-, HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino,
 C₃₋₇ cycloalkyl or C₁₋₄ alkyl-C(=O)NH-.

A further preferred group of compounds of Formula I includes compounds wherein

- 10 Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C(L);
 R¹ is H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₇ cycloalkyl, Q¹-,
 pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(C₁₋₈
 alkyl)amino, wherein said C₁₋₈ alkyl is optionally substituted with halo, C¹⁻³
 alkyl, hydroxy, oxo, C₁₋₄ alkoxy-, C₁₋₄ alkyl-S(O)m-, C₃₋₇ cycloalkyl-, cyano,
 15 indanyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹-, Q¹-C(O)-,
 Q¹-O-, Q¹-S-, Q¹-C₁₋₄ alkyl-O-, or C₁₋₄alkyl-C(O)-N(R³)-;
 Q¹ is a 5-12 membered monocyclic aromatic ring optionally containing up to 4
 heteroatoms selected from N and S, and is optionally substituted with halo, C₁₋₄
 alkyl, C₁₋₄ alkylsulfonyl and C₁₋₄ alkylC(=O)-;
 20 A is 5-6 membered monocyclic aromatic ring optionally substituted with halo,
 C₁₋₄ alkyl or C₁₋₄ alkoxy;
 B is C₃₋₇ cycloalkylene or C₁₋₆ alkylene optionally substituted with an oxo
 group or C₁₋₃ alkyl;
 W is NH, N-C₁₋₄ alkyl, O or N-OH;

R² is H or C₁₋₄ alkyl;

Z is 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄

5 alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkoxy, nitro, amino, cyano, R³C(=O)N(R⁴)-, C₁₋₄ alkyl-O(O=)C-, Q²-S(O)m-, Q²-O-, Q²-N(R³)- or Q²-;

L is halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, mono- or di-(C₁₋₄ alkyl)amino, cyano, HO-C₁₋₄ alkyl,

10 C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylC(=O)-, HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R³C(=O)N(R⁴)-, R³N(R⁴)C(=O)-, R³N(R⁴)S(O)m-, Q²-, Q²-C(=O)-, Q²-O-, Q²-C₁₋₄alkyl-O-, or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are

15 optionally replaced by oxygen atoms;
m is 0 or 2;

R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and

Q² is a 5 or 6 membered monocyclic aromatic ring, or a 8-12 membered tricyclic ring containing up to 3 heteroatoms selected from N and S, wherein said 5 or 6

20 membered monocyclic aromatic ring is optionally substituted with halo.

A further preferred group of compounds of Formula I includes compounds wherein

Y¹, Y², Y³ and Y⁴ are independently selected from N, CH and C(L);

R¹ is H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl or C₃₋₇ cycloalkyl, wherein said C₁₋₈ alkyl is optionally substituted with halo, C₁₋₃ alkyl, hydroxy, oxo, C₁₋₄ alkoxy-, C₁₋₄ alkyl-S(O)m-, C₃₋₇ cycloalkyl-, cyano, indanyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹-, Q¹-C(=O)-, Q¹-O-, Q¹-S-, Q¹-

5 C₁₋₄ alkyl-O-, or C₁₋₄alkyl-C(O)-N(R³)-;

Q¹ is a 5 or 6 membered monocyclic aromatic ring optionally containing up to 4 heteroatoms selected from N and S;

A is 5-6 membered monocyclic aromatic ring system optionally substituted with halo or C₁₋₄ alkyl;

10 B is or C₃₋₇ cycloalkylene or C₁₋₆ alkylene optionally substituted with an oxo group or C₁₋₃ alkyl;

W is NH, N-C₁₋₄ alkyl, O or N-OH;

R² is H or C₁₋₄ alkyl;

Z is 5-12 membered monocyclic or bicyclic aromatic ring optionally containing
 15 up to 3 heteroatoms selected from N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkoxy, nitro, amino, cyano, R³C(=O)N(R⁴)-, C₁₋₄ alkyl-O(O=)C-, Q²-S(O)m-, Q²-O-, Q²-N(R³)- or Q²-;

20 L is halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, cyano, HO-C₁₋₄ alkyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylC(=O), HO(O=)C-, C₁₋₄ alkyl-O(O=)C-, C₁₋₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R³C(=O)NR⁴-, R³N(R⁴)C(=O)-, R³N(R⁴)S(O)m-, Q²-, Q²-C(=O)-, Q²-O-, Q²-C₁₋₄alkyl-O-, or two adjacent L

groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;
m is 0 or 2;

- 5 R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and

Q² is 5 or 6 membered monocyclic aromatic ring or a 8-12 membered tricyclic ring optionally containing 1 sulfur atom wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo.

A further preferred group of compounds of Formula I includes compounds

- 10 wherein

Y¹, Y², Y³ and Y⁴ are independently selected from N, CH and C(L);

R¹ is C₁₋₅ alkyl or C₃₋₇ cycloalkyl, wherein said C₁₋₅ alkyl is optionally substituted with C₁₋₃ alkyl, hydroxy, oxo, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹-, or C₁₋₄alkyl-C(O)-N(H)-;

- 15 Q¹ is 5-12 membered monocyclic aromatic ring system optionally containing up to 2 heteroatoms selected from N and S,

A is 5-6 membered monocyclic aromatic ring system;

B is C₁₋₃ alkylene optionally substituted with C₁₋₃ alkyl;

W is NH, N-C₁₋₂ alkyl or O;

- 20 R² is H;

Z is 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5-12 membered monocyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, nitro, R³C(=O)N(R⁴)- or Q²-;

L is halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, cyano, HO-C₁₋₄ alkyl, acetyl, R³N(R⁴)C(=O)-, R³N(R⁴)S(O)m-, Q²-, Q²-C(=O)-, or two adjacent L groups are joined together to form a methylenedioxy group;

5 R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and

Q² is 5 or 6 membered monocyclic aromatic ring system.

A further preferred group of compounds of Formula I includes compounds wherein

Y¹, Y², Y³ and Y⁴ are independently selected from N, CH and C-L;

10 R¹ is C₁₋₅ alkyl optionally substituted with C₁₋₃ alkyl, hydroxy, oxo, 5 or 6 membered monocyclic aromatic ring, wherein said 5 or 6 membered monocyclic aromatic ring is containing 1 or 2 heteroatoms selected from N and S, or C₁₋

4alkyl-C(O)-N(R³)-;

A is phenyl;

15 B is C₁₋₂ alkylene optionally substituted with methyl;

W is NH, N-CH₃ or O;

R² is H;

Z is 5-10 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5-10 membered

20 monocyclic aromatic ring is optionally substituted with chloro, bromo, methyl, nitro, CH₃C(=O)NH-, tBuC(=O)NH- or phenyl; and

L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, -C(=O)NH₂, trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy

25 group.

A further preferred group of compounds of Formula I includes compounds wherein

Y^1 , Y^2 , Y^3 and Y^4 are independently selected from N, CH and C-L;

R^1 is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl,

5 thiazolylethyl methylamino, dimethylamino, pyrrolidinyl, pyridyl, or 1-acetylamino-1-methylethyl;

A is phenyl;

B is ethylene or propylene;

W is NH, N-CH₃ or O;

10 R^2 is H;

Z is phenyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, naphthyl or benzothienyl, said phenyl, pyrazolyl, thiazolyl, thiadiazolyl and thienyl being optionally substituted with one to three substituents independently selected from chloro, bromo, methyl, acetylamino, pivaloylamino, nitro and phenyl; and

15 L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, -C(=O)NH₂, trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methylethyl, or two adjacent L groups are joined together to form a methylenedioxy group.

20 A further preferred group of compounds of Formula I includes compounds wherein

Y^1 , Y^2 , Y^3 and Y^4 are selected from the group consisting of

a) Y^1 and Y^3 are C(L), Y^2 is CH and Y^4 is N;

b) Y^1 is CH, Y^2 and Y^3 are C(L) and Y^4 is N;

c) Y^1 , Y^2 and Y^3 are C(L) and Y^4 is N;

25 d) Y^1 and Y^3 are C(L), Y^2 is N and Y^4 is CH;

e) Y^1 is C(L) and Y^2 , Y^3 and Y^4 are CH;

- f) Y¹, Y³ and Y⁴ are CH, and Y² is C(L);
g) Y¹, Y² and Y³ are CH, and Y⁴ is C(L);
h) Y¹ and Y² are C(L), and Y³ and Y⁴ are CH;
i) Y¹ and Y³ are C(L), and Y² and Y⁴ are CH;
5 j) Y¹ and Y⁴ are CH, and Y² and Y³ are C(L);
k) Y¹ and Y² are CH, Y³ is C(L) and Y⁴ is N;
l) Y¹ and Y³ are CH, Y² is C(L) and Y⁴ is N;
m) Y¹, Y², Y³ and Y⁴ are CH;
n) Y¹ and Y² are C(L), Y³ is CH and Y⁴ is N;
10 o) Y¹, Y² and Y⁴ are CH, and Y³ is C(L);
p) Y¹ and Y² are C(L), Y³ is N and Y⁴ is CH;
q) Y¹ and Y³ are C(L), and Y² and Y⁴ are N;
r) Y¹ is C(L), Y² and Y³ are CH, and Y⁴ is N; and
s) Y² is C(L), Y¹ and Y³ are CH, and Y⁴ is N;
15 R¹ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl,
thiazolylethyl methylamino, dimethylamino, pyrrolidinyl, pyridyl, or 1-
acetyl-amino-1-methylethyl;
A is phenyl;
B is ethylene or propylene;
20 W is NH, N-CH₃ or O;
R² is H;
Z is phenyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, naphthyl or benzothienyl,
said phenyl, pyrazolyl, thiazolyl, thiadiazolyl and thienyl being optionally
substituted with one to three substituents independently selected from chloro,
25 bromo, methyl, acetyl-amino, pivaloylamino, nitro and phenyl; and

L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, –C(=O)NH₂, trifluoromethyloxy, methanesulfonyl, or 1-hydroxy-1-methylethyl, or two adjacent L groups are joined together to form a methylenedioxy group.

- 5 A further preferred group of compounds of Formula I includes compounds wherein

Y¹, Y², Y³ and Y⁴ are selected from the group consisting of

- a) Y¹ and Y³ are C(L), Y² is CH and Y⁴ is N;
 b) Y¹ is CH, Y² and Y³ are C(L) and Y⁴ is N;
 10 c) Y¹, Y² and Y³ are C(L) and Y⁴ is N;
 d) Y¹ and Y³ are C(L), Y² is N and Y⁴ is CH;
 e) Y¹ is C(L) and Y², Y³ and Y⁴ are CH;
 f) Y¹, Y³ and Y⁴ are CH, and Y² is C(L);
 g) Y¹, Y² and Y³ are CH, and Y⁴ is C(L);
 15 h) Y¹ and Y² are C(L), and Y³ and Y⁴ are CH;
 i) Y¹ and Y³ are C(L), and Y² and Y⁴ are CH; and
 j) Y¹ and Y⁴ are CH, and Y² and Y³ are C(L);

- R¹ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl, thiazolethyl methylamino, dimethylamino, pyrrolidinyl, pyridyl, or 1-acetylamino-1-methylethyl;
 20

A is phenyl;

B is ethylene or propylene;

W is NH, N-CH₃ or O;

R² is H;

Z is phenyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, naphthyl or benzothienyl, said phenyl, pyrazolyl, thiazolyl, thiadiazolyl and thienyl being optionally substituted with one to three substituents independently selected from chloro, bromo, methyl, acetylamino, pivaloylamino, nitro and phenyl; and

- 5 L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, –C(=O)NH₂, trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methylethyl, or two adjacent L groups are joined together to form a methylenedioxy group.

Preferred individual compounds of Formula I are following:

- 10 3-(4-{2-[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridine;
 3-(4-{2-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridine;
 15 N-[5-({2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl}amino)carbonyl]amino)sulfonyl)-1,3,4-thiadiazol-2-yl]acetamide;
 6-ethyl-5-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-5H-[1,3]dioxolo[4,5-*f*]benzimidazole;
 20 6-chloro-5-cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole;
 2-ethyl-5,7-dimethyl-3-(4-{2-[methyl(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3H-imidazo[4,5-*b*]pyridine;

2-ethyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino)propyl} phenyl)-3*H*-imidazo[4,5-*b*]pyridine;

2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-1-

5 methylethyl (4-methylphenyl)sulfonylcarbamate;

5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino)ethyl} phenyl)-2-propyl-3*H*-imidazo[4,5-*b*]pyridine;

2-isopropyl-5,7-dimethyl-3-(4-{2-[(4-

10 methylphenyl)sulfonyl]amino} carbonyl)amino)ethyl} phenyl)-3*H*-imidazo[4,5-*b*]pyridine;

2-butyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino)ethyl} phenyl)-3*H*-imidazo[4,5-*b*]pyridine;

15 2-isobutyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino)ethyl} phenyl)-3*H*-imidazo[4,5-*b*]pyridine;

5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino)ethyl} phenyl)-2-neopentyl-3*H*-imidazo[4,5-*b*]pyridine;

20 5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino)ethyl} phenyl)-2-[2-(1,3-thiazol-2-yl)ethyl]-3*H*-imidazo[4,5-*b*]pyridine;

3-{4-[2-({4-biphenylsulfonyl)amino} carbonyl) amino)ethyl]phenyl}-2-ethyl-

25 5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

2-ethyl-5,7-dimethyl-3-{4-[2-({[(1-naphthylsulfonyl)amino]carbonyl}amino)ethyl]phenyl}-3*H*-imidazo[4,5-*b*]pyridine;

- 5 2-ethyl-5,7-dimethyl-3-{4-[2-({[(2-naphthylsulfonyl)amino]carbonyl}amino)ethyl]phenyl}-3*H*-imidazo[4,5-*b*]pyridine;

2-ethyl-5,7-dimethyl-3-(4-{2-({[(2-thienyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine;

- 10 3-(4-{2-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

3-(4-{2-({[(4,5-dichloro-2-thienyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

- 15 3-{4-[2-({[(1-benzothien-2-yl)sulfonyl]amino}carbonyl)amino}ethyl]phenyl}-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

3-(4-{2-({[(2-chlorophenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

- 20 2-ethyl-5,6-dimethyl-3-(4-{2-({[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine;

5,6-dichloro-2-ethyl-3-(4-{2-({[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine;

- 25 5-chloro-2-ethyl-7-methyl-3-(4-{2-({[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine;

6-cyano-2-ethyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine;

2-ethyl-4,6-dimethyl-1-(4-{2-[(4-

- 5 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-imidazo[4,5-*c*]pyridine;

4-methyl-2-ethyl-3-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)benzimidazole;

7-chloro-2-ethyl-3-(4-{2-[(4-

- 10 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)benzimidazole;

5-methoxy-2-ethyl-3-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)benzimidazole;

5-acetyl-2-ethyl-3-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)benzimidazole;

- 15 5-cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole;

2-ethyl-5-hydroxy-1-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-

- 20 benzimidazole;

2-ethyl-4,5-dimethyl-1-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-

benzimidazole;

4,6-dimethyl-2-ethyl-3-(4-{2-[(4-

- 25 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)benzimidazole;

5,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-1*H*-benzimidazole;

5,6-dichloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-1*H*-benzimidazole;

2-[4-(5,6-dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl-(4-methylphenyl)sulfonyl carbamate;

6-chloro-5-trifluoromethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-1*H*-benzimidazole;

4-(6-chloro-2-ethyl-5-trifluoromethyl-1*H*-benzimidazol-1-yl)phenethyl-(4-methylphenyl)sulfonyl carbamate;

5-chloro-6-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-1*H*-benzimidazole;

6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-1*H*-benzimidazole-5-carboxamide;

2-ethyl-3-{4-[2-({3-[hydroxy(oxido)amino]phenyl} sulfonyl)amino]carbonyl} aminoethyl} phenyl]-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

3-(4-{2-[(4-chlorophenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

n-[4-({2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl} amino)carbonyl]amino} sulfonyl]phenyl]-2,2-dimethylpropanamide;

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3-(4-{2-[(3-chlorophenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

3-(4-{2-[(3-chlorophenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

5 3-(4-{2-[(5-chloro-2-thienyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

3-(4-{2-[(5-bromo-2-thienyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

10 3-(4-{2-[(2-bromophenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

3-{4-[2-[(4-chloro-3-nitrophenyl)sulfonyl]amino]carbonyl]amino}ethyl}phenyl}-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;

2-[4-(2-ethyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-

15 methylphenyl)sulfonylcarbamate;

2-{4-[5,7-dimethyl-2-(methylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;

N-{[(2-{4-[5,7-dimethyl-2-(methylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;

20 *N*-{[(2-{4-[2-ethyl-5-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;

2-ethyl-4,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide;

25 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (2-chlorophenyl)sulfonylcarbamate;

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2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-2-pyridinyl} ethyl (4-methylphenyl)sulfonylcarbamate;

2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl (5-methyl-2-pyridinyl)sulfonylcarbamate;

5 2-{4-[6-chloro-2-(1*H*-pyrazol-3-yl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl (4-methylphenyl)sulfonylcarbamate;

2-{4-[6-chloro-2-(4-pyridinyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl (4-methylphenyl)sulfonylcarbamate;

10 2-{4-[5-(aminocarbonyl)-6-chloro-2-ethyl-1*H*-benzimidazol-1-yl]phenyl} ethyl (4-methylphenyl)sulfonylcarbamate;

N-{[(2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;

2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl (4-methylphenyl)sulfonylcarbamate;

15 *N*-{[(2-{4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl}ethyl) amino]carbonyl}-2-thiophenesulfonamide;

2-[4-(4,6-dimethyl-2-phenyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;

20 2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;

2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)sulfonylcarbamate;

2-{4-[4,6-dimethyl-2-(3-phenylpropyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]phenyl} ethyl (4-methylphenyl)sulfonylcarbamate;

25 2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl (4-methylphenyl)sulfonylcarbamate;

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(1*S*)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}-1-methylethyl (4-methylphenyl)sulfonylcarbamate;

2-{6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-3-pyridinyl} ethyl (4-methylphenyl)sulfonylcarbamate;

- 5 *N*-{[(2-{4-[6-chloro-2-(1-hydroxy-1-methylethyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl)amino]carbonyl}-4-methylbenzenesulfonamide; and

N-{[(2-{4-[5,7-dimethyl-2-(1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]phenyl} ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;

- 10 2-{4-[2-(1,1-dimethylethyl)-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]phenyl} ethyl (4-methylphenyl)sulfonylcarbamate;

2-{4-[2-[1-(acetylamino)-1-methylethyl]-6-chloro-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl (4-methylphenyl)sulfonylcarbamate;

- 6-chloro-2-ethyl-1-(4-{2-[methyl({[(4-methylphenyl)sulfonyl]amino} carbonyl)amino]ethyl} phenyl)-1*H*-benzimidazole-5-carboxamide; and salts thereof.
- 15

Most preferred individual compounds of Formula I are following:

6-ethyl-5-(4-{2-[(4-

- 20 methylphenyl)sulfonyl]amino} carbonyl)amino]ethyl} phenyl)-5*H*-[1,3]dioxolo[4,5-*f*]benzimidazole;

6-chloro-5-cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino]ethyl} phenyl)-1*H*-benzimidazole; 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-1-

- 25 methylethyl (4-methylphenyl)sulfonylcarbamate;

- 5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-2-[2-(1,3-thiazol-2-yl)ethyl]-3*H*-imidazo[4,5-*b*]pyridine;
- 2-ethyl-5,7-dimethyl-3-(4-{2-[(2-thienyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-3*H*-imidazo[4,5-*b*]pyridine;
- 3-(4-{2-[(2-chlorophenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine;
- 2-ethyl-5,6-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-3*H*-imidazo[4,5-*b*]pyridine;
- 5,6-dichloro-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-3*H*-imidazo[4,5-*b*]pyridine;
- 2-ethyl-4,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-1*H*-imidazo[4,5-*c*]pyridine;
- 5-methoxy-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)benzimidazole;
- 5-acetyl-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)benzimidazole;
- 5-cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-1*H*-benzimidazole;
- 2-ethyl-5-hydroxy-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)aminoethyl} phenyl)-1*H*-benzimidazole;

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2-ethyl-4,5-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole;

- 4-(6-chloro-2-ethyl-5-trifluoromethyl-1*H*-benzimidazol-1-yl)phenethyl-(4-methylphenyl)sulfonylcarbamate; and
- 5 6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide;
- 2-[4-(2-ethyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;
- 10 2-[4-[5,7-dimethyl-2-(methylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;
- N*-{[(2-{4-[5,7-dimethyl-2-(methylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;
- 15 *N*-{[(2-{4-[2-ethyl-5-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;
- 2-ethyl-4,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide;
- 20 2-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl]ethyl (2-chlorophenyl)sulfonylcarbamate;
- 2-[5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-2-pyridinyl]ethyl (4-methylphenyl)sulfonylcarbamate;
- 2-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl]ethyl (5-methyl-2-pyridinyl)sulfonylcarbamate;
- 25 2-[4-[6-chloro-2-(1*H*-pyrazol-3-yl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;

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2-{4-[6-chloro-2-(4-pyridinyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;

2-{4-[5-(aminocarbonyl)-6-chloro-2-ethyl-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;

5 *N*-{[(2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;

2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;

10 *N*-{[(2-{4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl}ethyl)amino]carbonyl}-2-thiophenesulfonamide;

2-[4-(4,6-dimethyl-2-phenyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;

2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;

15 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)sulfonylcarbamate;

2-{4-[4,6-dimethyl-2-(3-phenylpropyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;

20 2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;

(1*S*)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}-1-methylethyl (4-methylphenyl)sulfonylcarbamate;

2-{6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-3-pyridinyl}ethyl (4-methylphenyl)sulfonylcarbamate;

25 *N*-{[(2-{4-[6-chloro-2-(1-hydroxy-1-methylethyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;
and

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N-{[(2-{4-[5,7-dimethyl-2-(1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;
2-{4-[2-(1,1-dimethylethyl)-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;
5 2-{4-[2-[1-(acetylamino)-1-methylethyl]-6-chloro-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;
6-chloro-2-ethyl-1-(4-{2-[methyl({[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide; and
10 salts thereof.

Synthesis of Formula I Compounds.

Representative Formula I compounds and methods of synthesizing Formula 1 compounds are described in the following Examples 1-380.

15 Additional general synthesis schemes are described in U.S. provisional application 60/241,825, filed October 19, 2000, and in Akiyoshi et al., a non-provisional application filed on approximately October 10, 2001 and entitled "Aryl or Heteroaryl Fused Imidazole Compounds as Anti-Inflammatory and Analgesic Agents."

20 Unless stated otherwise, all operations described in the Examples below were carried out at room or ambient temperature, that is, in the range of 18-25 °C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath temperature of up to 60 °C; reactions were monitored by thin layer chromatography (TLC) and reaction times are given for
25 illustration only; melting points (mp) given are uncorrected (polymorphism may result in different melting points); the structure and purity of all isolated compounds were assured by at least one of the following techniques: TLC

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(Merck silica gel 60 F₂₅₄ precoated TLC plates), mass spectrometry, nuclear magnetic resonance (NMR), infrared red absorption spectra (IR) or microanalysis. Yields are given for illustrative purposes only. Flash column chromatography was carried out using Merck silica gel 60 (230–400 mesh

- 5 ASTM). Low-resolution mass spectral data (EI) were obtained on a Automass 120 (JEOL) mass spectrometer. Low-resolution mass spectral data (ESI) were obtained on a Quattro II (Micromass) mass spectrometer or a ZMD (Micromass). NMR data was determined at 270 MHz (JEOL JNM-LA 270 spectrometer) or 300 MHz (JEOL JNM-LA300 spectrometer) using deuterated chloroform
- 10 (99.8% D) or dimethylsulfoxide (99.9% D) as solvent unless indicated otherwise, relative to tetramethylsilane (TMS) as internal standard in parts per million (ppm); conventional abbreviations used are: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br. = broad, etc. IR spectra were measured by a Shimadzu infrared spectrometer (IR-470). Chemical symbols
- 15 have their usual meanings; bp (boiling point), mp (melting point), L (liter(s)), mL (milliliter(s)), g (gram(s)), mg (milligram(s)), mol (moles), mmol (millimoles), eq. (equivalent(s)), quant. (quantitative yield).

EXAMPLE 1

- 20 2-ETHYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-b]PYRIDINE

STEP 1. 4,6-Dimethyl-3-nitro-2(1H)-pyridinone

- A mixture of ethyl nitroacetate (80.0 g, 601 mmol) in ammonium hydroxide
- 25 (25% NH₃ in water, 400 mL) was stirred at room temperature for 3 days, and then the solution was concentrated by air-drying. The residue was dissolved in water (450 mL). To the solution was added 2,4-pentanedione (73.1 g, 730

mmol), pyridine (16.2 mL, 200 mmol) and acetic acid (11.4 mL, 200 mmol), and the mixture was stirred for an additional 7 days. The resulting precipitates were collected by filtration and dried under reduced pressure to give 35.0 g (35%) of the title compound as yellow solids: $^1\text{H-NMR}$ (DMSO-d_6) δ 12.44 (1H, br.s),

6.06 (1H, s), 2.19 (3H, s), 2.13 (3H, s).

STEP 2. 2-Chloro-4,6-dimethyl-3-nitropyridine

A mixture of 4,6-dimethyl-3-nitro-2(1H)-pyridinone (step 1, 10.0 g, 29.7 mmol) in phosphorus oxychloride (35 mL, 187.3 mmol) was stirred at 95 °C for 3 h, then cooled to 45 °C. The excess amount of phosphorus oxychloride was

removed by distillation under reduced pressure at 45 °C. The residue was cooled to room temperature, and diluted with dichloromethane (75 mL). The resulting solution was cooled to 0°C, and 2N hydrochloric acid (50 mL) was added

dropwise into the solution. The organic layer was separated, and washed with 2N hydrochloric acid (4 x 25 mL), 2N aqueous NaOH (2 x 50 mL) and brine (50

mL). The organic phase was dried (MgSO_4) and concentrated under reduced pressure to give 10.0 g (90%) of the title compound as white solids: $^1\text{H-NMR}$ (CDCl_3) δ 7.07 (1H, s), 2.56 (3H, s), 2.35 (3H, s).

STEP 3. 2-[4-[(4,6-Dimethyl-3-nitro-2-pyridinyl)amino]phenyl]ethanol

A mixture of 2-chloro-4,6-dimethyl-3-nitropyridine (step 2, 1.3 g, 7.0 mmol) and 4-aminophenylethyl alcohol (1.4 g, 10.2 mmol) was placed in a sealed tube and heated at 150 °C for 3 h. The reaction mixture was cooled and purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (2:1) to

afford 1.6 g (80%) of the title compound as orange solids: $^1\text{H-NMR}$ (CDCl_3) δ 9.55 (1H, br.s), 7.57 (2H, d, $J=8.4$ Hz), 7.20 (2H, d, $J=8.4$ Hz), 6.52 (1H, s), 3.84

(2H, t, $J=6.4$ Hz), 2.85 (2H, t, $J=6.4$ Hz), 2.54 (3H, s), 2.42 (3H, s).

STEP 4. 2-[4-[(3-Amino-4,6-dimethyl-2-pyridinyl)amino]phenyl]ethanol

To a stirred solution of 2-{4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol (step 3, 1.6 g, 5.6 mmol) in ethyl acetate (15 mL) was added 10% Pd-C (160 mg). The mixture was stirred at room temperature for 6 h under hydrogen atmosphere. The palladium catalyst was removed by filtration and washed with ethanol (100 mL). The filtrate was concentrated under reduced pressure to afford 1.3 g (92%) of the title compound as pale yellow solids: ¹H-NMR (CDCl₃) δ 7.10 (4H, s), 6.61 (1H, s), 3.81 (2H, t, J=6.4 Hz), 2.80 (2H, t, J=6.4 Hz), 2.36 (3H, s), 2.19 (3H, s).

STEP 5. 2-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate

To a stirred suspension of 2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethanol (step 4, 1.3 g, 5.1 mmol) in toluene (30 mL) was added dropwise propionyl chloride (990 mg, 10.7 mmol) at 0 °C, and the reaction mixture was heated at reflux temperature for 2 h. After cooling, the mixture was poured into water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with 2N aqueous NaOH (50 mL) and brine (50 mL), then dried (MgSO₄). Removal of solvent gave 1.8 g (quant.) of the title compound as brown solids: ¹H-NMR (CDCl₃) δ 7.41 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz), 6.90 (1H, s), 4.37 (2H, t, J=6.9 Hz), 3.04 (2H, t, J=6.9 Hz), 2.82 (2H, q, J=7.6 Hz), 2.65 (3H, s), 2.52 (3H, s), 2.35 (2H, q, J=7.6 Hz), 1.27 (3H, t, J=7.6 Hz), 1.14 (3H, t, J=7.6 Hz).

STEP 6. 2-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol

To a solution of 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate (step 5, 1.75 g, 5.1 mmol) in methanol/THF (v/v, 1:1, 28 mL) was added 4N aqueous LiOH (4.6 mL, 18.4 mmol) and the resulting mixture was stirred at room temperature. After 3 h, the mixture was

concentrated. The residue was dissolved in water (30 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (50 mL), dried (MgSO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (gradient elution from 2:1 to 0:1) to afford 1.3 g (86%) of the title compound as pale brown solids: ¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 6.91 (1H, s), 3.81-3.75 (2H, m), 3.47 (1H, br.s), 2.92 (2H, t, J=6.9 Hz), 2.81 (2H, q, J=7.6 Hz), 2.66 (3H, s), 2.51 (3H, s), 1.27 (3H, t, J=7.6 Hz).

STEP 7. 3-[4-(2-Chloroethyl)phenyl]-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridine

To a solution of 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 6, 2.2 g, 7.4 mmol) in toluene (40 mL) was added thionyl chloride (2.0 mL, 23.6 mmol), and the resulting mixture was stirred at 80 °C for 3 h. The volatile components were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (gradient elution from 2:1 to 1:1) to afford 2.1 g (90%) of the title compound as white solids: ¹H-NMR (CDCl₃) δ 7.41 (2H, d, J=8.4 Hz), 7.35 (2H, d, J=8.4 Hz), 6.90 (1H, s), 3.78 (2H, t, J=7.4 Hz), 3.15 (2H, t, J=7.4 Hz), 2.83 (2H, q, J=7.6 Hz), 2.71 (3H, s), 2.54 (3H, s), 1.28 (3H, t, J=7.6 Hz).

STEP 8. 2-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

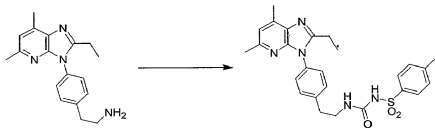
To a stirred solution of 3-[4-(2-chloroethyl)phenyl]-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridine (step 7, 2.8 g, 9.0 mmol) and KI (1.5 g, 9.0 mmol) in DMF (50 mL) was added sodium azide (1.2 g, 18.0 mmol), and then the resulting mixture was stirred overnight at 100 °C. The reaction mixture was poured into water (100 mL), and extracted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), then dried

(Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to afford 2.35 g (85%) of the title compound as white solids: ¹H-NMR (CDCl₃) δ 7.41 (2H, d, J=8.4 Hz), 7.35 (2H, d, J=8.4 Hz), 6.90 (1H, s), 3.59 (2H, t, J=7.1 Hz), 2.99 (2H, t, J=7.1 Hz), 2.83 (2H, q, J=7.6 Hz), 2.65 (3H, s), 2.52 (3H, s), 1.27 (3H, t, J=7.6 Hz).

STEP 9. 2-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylamine

To a solution of 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl azide (step 8, 2.35 g, 7.3 mmol) in methanol (50 mL) was added 10% Pd-C (200 mg). The resulting mixture was stirred for 4 h under hydrogen atmosphere. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol/triethylamine (100:5:1) to afford 2.01 g (94%) of the title compound as white solids: ¹H-NMR (CDCl₃) δ 7.39 (2H, d, J=8.4 Hz), 7.32 (2H, d, J=8.4 Hz), 6.90 (1H, s), 3.05 (2H, t, J=7.3 Hz), 2.88-2.78 (4H, m), 2.65 (3H, s), 2.51 (3H, s), 1.28 (3H, t, J=7.6 Hz).

STEP 10. 2-Ethyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl)phenyl)-3H-imidazo[4,5-b]pyridine



To a solution of 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 9, 1.2 g, 4.0 mmol) in dichloromethane (15 mL) was added *p*-toluenesulfonyl isocyanate (805 mg, 4.0 mmol). The resulting mixture was stirred at room temperature for 3 h. After removal of solvent, the residue

was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol (20:1) to afford 1.10 g (56%) of the title compound as white solids: ¹H-NMR (CDCl₃) δ 7.85 (2H, d, J=8.2 Hz), 7.32 (2H, d, J=8.2 Hz), 7.23 (2H, d, J=8.4 Hz), 7.16 (2H, d, J=8.4 Hz), 6.91 (1H, s), 6.12 (1H, br.s), 3.55-3.46 (2H, m), 2.85 (2H, t, J=6.3 Hz), 2.74-2.64 (5H, m), 2.42 (3H, s), 2.41 (3H, s), 1.21 (3H, t, J=7.6 Hz).

EXAMPLE 2

2-ETHYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, SODIUM SALT

To a solution of 2-ethyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine (Example 1, 5.0 g, 10.2 mmol) in methanol (20 mL) was added 2*N* aqueous NaOH (5.1 mL, 10.2 mmol). The resulting mixture was stirred at room temperature for 5 min and concentrated. The residual solids were collected by filtration and dried under reduced pressure at 50 °C to afford the title compound as white solids: ¹H-NMR (DMSO-*d*₆) δ 7.60 (2H, d, J=8.2 Hz), 7.31-7.39 (4H, m), 7.14 (2H, d, J=8.2 Hz), 6.96 (1H, s), 3.15 (2H, br.s), 2.66-2.75 (4H, m), 2.53 (3H, s), 2.40 (3H, s), 2.28 (3H, s), 1.20 (3H, t, J=7.6 Hz).

EXAMPLE 3

2-[4-(2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE-3-YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

To a solution of 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 6 of Example 1, 300 mg, 1.0 mmol) in dichloromethane (10 mL) was added *p*-toluenesulfonyl isocyanate (237 mg, 1.2 mmol). The resulting mixture was stirred at room temperature overnight. After removal of solvent, the residual solids were recrystallized from ethyl acetate to afford 454 mg (92%) of the title compound as white solids: ¹H-NMR (CDCl₃) δ 7.93 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz), 7.22 (4H, s), 6.92 (1H, s), 4.87 (1H, br.s), 4.35 (2H, t, J=6.6 Hz), 2.96 (2H, t, J=6.6 Hz), 2.78 (2H, q, J=7.7 Hz), 2.66 (3H, s), 2.50 (3H, s), 2.43 (3H, s), 1.24 (3H, t, J=7.7 Hz).

EXAMPLE 4

2-ETHYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYL(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE

To a stirred solution of 2-ethyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine (Example 1, 200 mg, 0.41 mmol) in THF (10 mL) was added dropwise a solution of lithium diisopropylamide (LDA) (2.0 N in heptane/hexane/ethylbenzene, 0.8 mL, 1.6 mmol) with ice-cooling over a period of 10 min. After completion of the addition, the stirring was continued for an additional 20 min at the same temperature. To the resulting mixture was added dropwise MeI (0.5 mL) at 0 °C, and stirred at room temperature for 15 h. The mixture was poured into a solution of phosphate buffer (100 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with brine (50 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on silica gel eluting with dichloromethane/methanol (10:1) to give 10 mg (5%) of the title compound as a colorless oil: ¹H-NMR (CDCl₃) δ 7.64 (2H, d, J=8.3 Hz), 7.53-7.25 (7H, m), 6.89 (1H, s), 3.65-3.55 (2H, m), 3.14

(3H, s), 2.96 (2H, t, J=6.7 Hz), 2.82 (2H, q, J=7.6 Hz), 2.66 (3H, s), 2.50 (3H, s), 2.40 (3H, s), 1.25 (3H, t, J=7.6 Hz).

EXAMPLE 5

2-ETHYL-5,7-DIMETHYL-3-(4-{2-[METHYL({[(4-

5 METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3H-
IMIDAZO[4,5-*b*]PYRIDINE

STEP 1. *N*-{2-[4-(2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-
yl)phenyl]ethyl}-*N*-methylamine

A mixture of 3-[4-(2-chloroethyl)phenyl]-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-
 10 *b*]pyridine (step 7 of Example 1, 627 mg, 9.0 mmol), a solution of methylamine
 (40% in methanol, 6 mL) and water (6 mL) was placed in a sealed tube and
 heated overnight at 130 °C. The reaction mixture was partitioned between
 dichloromethane (50 mL) and water (50 mL). The organic phase was separated
 and the aqueous phase was extracted with dichloromethane (50 mL). The
 15 combined organic extracts were washed with brine (50 mL) and dried (Na₂SO₄).
 After removal of solvent, the crude product was purified by flash column
 chromatography on silica gel eluting with dichloromethane/methanol (5:1) to
 afford 523 mg (85%) of the title compound as white solids: ¹H-NMR (CDCl₃) δ
 7.41 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=8.3 Hz), 6.90 (1H, s), 4.73 (1H, br.s), 2.93
 20 (4H, s), 2.82 (2H, q, J=7.5 Hz), 2.65 (3H, s), 2.51 (3H, s), 2.49 (3H, s), 1.28 (3H,
 t, J=7.5 Hz).

STEP 2. 2-Ethyl-5,7-dimethyl-3-(4-{2-[methyl({[(4-
methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-
b]pyridine

25 To a solution of *N*-{2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-
 yl)phenyl]ethyl}-*N*-methylamine (step 1, 523 mg, 1.7 mmol) in dichloromethane
 (10 mL) and triethylamine (2 mL) was added *p*-toluenesulfonyl isocyanate (400

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mg, 2.0 mmol). The resulting reaction mixture was stirred at room temperature for 6 h. After removal of solvent, the residue was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol (10:1) to afford 358 mg (42%) of the title compound as white solids: $^1\text{H-NMR}$ (CDCl_3) δ 7.93 (2H, d, $J=8.3$ Hz), 7.31 (2H, d, $J=8.4$ Hz), 7.24 (2H, d, $J=8.3$ Hz), 7.14 (2H, d, $J=8.4$ Hz), 6.92 (1H, s), 3.66-3.49 (2H, m), 3.51 (3H, s), 2.93-2.70 (4H, m), 2.65 (3H, s), 2.50 (3H, s), 2.38 (3H, s), 1.24 (3H, t, $J=7.2$ Hz).

EXAMPLE 6

2-ETHYL-5,7-DIMETHYL-3-(4-{2-[(4-

METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}PROPYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE

STEP 1. 1-(4-Aminophenyl)-2-propanol

A mixture of 1-(4-nitrophenyl)-2-propanol (Schadt, F.L.; et al. *J.Am.Chem.Soc.*, 1978, 100, 228., 2.2 g, 12.3 mmol), iron powder (3.3 g, 59.1 mmol), ammonium chloride (370 mg, 6.9 mmol), ethanol (48 mL) and water (24 mL) was heated at reflux temperature for 2 h. The mixture was cooled and filtered through a pad of Celite. The filtrate was concentrated. The residue was diluted with ethyl acetate (200 mL) and washed with water (2 x 100 mL). The organic layer was dried (MgSO_4), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to afford 1.45 g (78 %) of the title compound as a yellow oil: $^1\text{H-NMR}$ (CDCl_3) δ 7.00 (2H, d, $J=8.6$ Hz), 6.64 (2H, d, $J=8.8$ Hz), 3.99-3.89 (1H, m), 3.60 (2H, br s), 2.72-2.52 (2H, m), 1.22 (3H, d, $J=6.2$ Hz).

STEP 2. 1-{4-[4-(4,6-Dimethyl-3-nitro-2-pyridinyl)amino]phenyl}-2-propanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 1-(4-aminophenyl)-2-propanol (step 1) and 2-chloro-4,6-dimethyl-3-nitropyridine (step 2 of Example 1).

¹H-NMR (CDCl₃) δ 9.59 (1H, br.s), 7.58 (2H, d, J=8.4 Hz), 7.20 (2H, d, J=8.4 Hz), 6.53 (1H, s), 4.13-4.01 (1H, m), 2.82-2.64 (2H, m), 2.55 (3H, s), 2.44 (3H, s), 1.25 (3H, d, J=6.2 Hz).

STEP 3. 1-{4-[(3-Amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}-2-propanol

A mixture of 1-{4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}-2-propanol (step 2, 500 mg, 1.66 mmol), iron powder (440 mg, 7.88 mmol), ammonium chloride (80 mg, 1.5 mmol) in ethanol/water (v/v, 31:8, 39 mL) was heated at reflux temperature for 2 h. The mixture was cooled and filtered through a pad of Celite. The filtrate was concentrated. The residue was diluted with dichloromethane (200 mL) and washed with water (2 x 100 mL). The organic layer was dried (MgSO₄), and concentrated. Removal of solvent gave 450 mg (quant.) of the title compound as brown solids: TLC Rf 0.10 (hexane/ethyl acetate = 1:1).

STEP 4. 2-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}-2-propanol (step 3) and propionyl chloride.

TLC Rf = 0.30 (hexane/ethyl acetate = 1:1).

STEP 5. 1-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-2-propanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl propionate (step 4).

¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.0 Hz), 6.91 (1H, s), 4.16-4.07 (1H, m), 2.90-2.76 (4H, m), 2.66 (2H, s), 2.52 (3H, s), 1.32-1.22 (6H, m).

STEP 6. 3-[4-(2-Chloropropyl)phenyl]-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 1-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-2-propanol (step 5).

TLC R_f = 0.50 (hexane/ethyl acetate = 1:1).

STEP 7. 2-[4-(2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-1-methylethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[4-(2-chloropropyl)phenyl]-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (step 6).

¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.4 Hz), 6.91 (1H, s), 3.81-3.74 (1H, m), 2.95-2.79 (4H, m), 2.66 (3H, s), 2.52 (3H, s), 1.35 (3H, d, J=6.6 Hz), 1.27 (3H, t, J=7.5 Hz).

STEP 8. 1-[4-(2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-2-propanamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-1-methylethyl azide (step 7).

¹H-NMR (CDCl₃) δ 7.40-7.31 (4H, m), 6.90 (1H, s), 3.31-3.20 (1H, m), 2.87-2.77 (3H, m), 2.66-2.58 (4H, m), 2.52 (3H, s), 1.28 (3H, t, J=8.3 Hz), 1.19 (3H, d, J=6.8 Hz).

STEP 9. 2-Ethyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}propyl)phenyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-2-propanamine (step 8).

mp 128 °C; MS (ESI) m/z 506.19 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 7.74 (2H, d, J=8.3 Hz), 7.30-7.19 (6H, m), 6.90 (1H, s), 4.08-4.02 (1H, m), 2.84-2.72 (4H, m), 2.65 (3H, s), 2.48 (3H, s), 2.32 (3H, s), 1.20-1.13 (6H, m).

EXAMPLE 7

5 2-[4-(2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-*b*]PYRIDIN-3-
YL)PHENYL]-1-METHYLETHYL (4-
METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 1-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-2-propanol (step 5 of Example 6).

mp 108 °C; MS (ESI) m/z 507.18 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 7.91 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.3 Hz), 7.23 (4H, s), 6.91 (1H, s), 5.10-5.04 (1H, m), 2.95-2.76 (4H, m), 2.65 (3H, s), 2.50 (3H, s), 2.41 (3H, s), 1.28-1.21 (6H, m).

EXAMPLE 8

15 5,7-DIMETHYL-3-(4-{2-[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PH
ENYL)-2-PROPYL-3H-IMIDAZO[4,5-*b*]PYRIDINE

STEP 1. 2-[4-(5,7-Dimethyl-2-propyl-3H-imidazo[4,5-*b*]pyridin-3-
yl)phenyl]ethyl butyrate

20 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl} ethanol (step 4 of Example 1) and butyryl chloride.

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.2 Hz), 7.32 (2H, d, J=8.2 Hz), 6.92 (1H, s), 4.39 (2H, t, J=6.4 Hz), 3.09 (2H, t, J=6.4 Hz), 2.77 (2H, t, J=7.7 Hz), 2.66 (3H, s), 2.52 (3H, s), 2.32 (2H, t, J=7.7 Hz), 1.81-1.58 (4H, m), 1.00-0.86 (6H, m).

STEP 2. 2-[4-(5,7-Dimethyl-2-propyl-3H-imidazo[4,5-*b*]pyridin-3-
yl)phenyl]ethanol

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The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl butyrate (step 1).

¹H-NMR (CDCl₃) δ 7.43 (2H, d, J=8.0 Hz), 7.32 (2H, d, J=8.0 Hz), 6.90 (1H, s), 4.00-3.89 (2H, m), 2.97 (2H, t, J=6.4 Hz), 2.78 (2H, t, J=7.8 Hz), 2.65 (3H, s), 2.51 (3H, s), 1.80-1.64 (2H, m), 0.92 (3H, t, J=7.4 Hz).

STEP 3. 3-[4-(2-Chloroethyl)phenyl]-5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 2).

MS (EI) *m/z* 327 (M⁺).

STEP 4. 2-[4-(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[4-(2-chloroethyl)phenyl]-5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridine (step 3).

MS (EI) *m/z* 334 (M⁺); ¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.4 Hz), 6.91 (1H, s), 3.60 (2H, t, J=7.2 Hz), 3.00 (2H, t, J=7.2 Hz), 2.77 (2H, t, J=7.8 Hz), 2.65 (3H, s), 2.52 (3H, s), 1.75-1.62 (2H, m), 0.90 (3H, t, J=7.4 Hz).

STEP 5. 2-[4-(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 4).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 6.88 (1H, s), 3.89 (2H, br.s), 3.18 (2H, t, J=6.8 Hz), 3.01 (2H, t, J=6.8 Hz), 2.75 (2H, t, J=7.5 Hz), 2.64 (3H, s), 2.48 (3H, s), 1.78-1.63 (2H, m), 0.90 (3H, t, J=7.3 Hz).

STEP 6. 5,7-Dimethyl-3-(4-{2-[(4-

5 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-propyl-3H-
imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(5,7-dimethyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylamine (step 5).

10 ¹H-NMR (CDCl₃) δ 7.86 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.3 Hz), 7.23 (2H, d, J=8.3 Hz), 7.16 (2H, d, J=8.3 Hz), 6.90 (1H, s), 6.10 (1H, br.s), 3.58-3.46 (2H, m), 2.87 (2H, t, J=6.4 Hz), 2.71-2.59 (5H, m), 2.42 (3H, s), 2.40 (3H, s), 1.74-1.61 (2H, m), 0.89 (3H, t, J=7.0 Hz).

EXAMPLE 9

15 2-ISOPROPYL-5,7-DIMETHYL-3-(4-{2-[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-3H-IMIDAZO[4,5-b]PYRIDINE

STEP 1. 5-Bromo-4,6-dimethyl-3-nitro-2-pyridinol

To a solution of 5-bromo-4,6-dimethyl-3-nitro-2-pyridinylamine (Heitsch, H.; et
20 al. *Bioorg. Med. Chem.* 1997, 5, 673., 2.0 g, 8.1 mmol) in trifluoroacetic acid/water (v/v, 2:1, 30 mL) was added sodium nitrite (1.1 g, 16 mmol) in small portions at room temperature, and then the reaction mixture was stirred overnight. The resulting precipitates were collected by filtration, washed with water, and dried under reduced pressure to give 2.2 g (quant.) of the title
25 compound: ¹H-NMR (CDCl₃) δ 2.53 (3H, s), 2.38 (3H, s).

STEP 2. 3-Bromo-6-chloro-2,4-dimethyl-5-nitropyridine

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The title compound was prepared according to the procedure described in step 2 of Example 1 from 5-bromo-4,6-dimethyl-3-nitro-2-pyridinol (step 1).

¹H-NMR (CDCl₃) δ 2.72 (3H, s), 2.41 (3H, s).

STEP 3. 2-{4-[(5-Bromo-4,6-dimethyl-3-nitro-2-

pyridinyl)amino]phenyl} ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 3-bromo-6-chloro-2,4-dimethyl-5-nitropyridine (step 2) and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 8.66 (1H, br.s), 7.51 (2H, d, J=8.4 Hz), 7.22 (2H, d, J=8.4 Hz), 3.90-3.77 (2H, m), 2.88 (2H, t, J=6.5 Hz), 2.65 (3H, s), 2.59 (3H, s).

STEP 4. 2-{4-[(3-Amino-5-bromo-4,6-dimethyl-2-

pyridinyl)amino]phenyl} ethanol

The title compound was prepared according to the procedure described in step 4 of Example 1 from 2-{4-[(5-bromo-4,6-dimethyl-3-nitro-2-

pyridinyl)amino]phenyl} ethanol (step 3).

¹H-NMR (CDCl₃) δ 7.12 (4H, s), 6.21 (1H, s), 3.38 (1H, br.s), 3.82 (2H, t, J=6.5 Hz), 2.80 (2H, t, J=6.5 Hz), 2.54 (3H, s), 2.38 (3H, s).

STEP 5. 2-[4-(6-Bromo-2-isopropyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl 2-methylpropanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-5-bromo-4,6-dimethyl-2-pyridinyl)amino]phenyl} ethanol (step 4) and isobutyryl chloride.

MS (EI) m/z 457 (M⁺).

STEP 6. 2-[4-(6-Bromo-2-isopropyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-bromo-2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl 2-methylpropanoate (step 5).

¹H-NMR (CDCl₃) δ 7.45 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.3 Hz), 3.96 (2H, t, J=7.3 Hz), 3.15-3.03 (1H, m), 2.97 (2H, t, J=7.3 Hz), 2.76 (3H, s), 2.67 (3H, s), 1.34 (6H, d, J=6.8 Hz).

STEP 7. 6-Bromo-3-[4-(2-chloroethyl)phenyl]-2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(6-bromo-2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 6).

¹H-NMR (CDCl₃) δ 7.43 (2H, d, J=8.3 Hz), 7.32 (2H, d, J=8.3 Hz), 3.81 (2H, t, J=7.3 Hz), 3.19 (2H, t, J=7.3 Hz), 3.15-3.02 (1H, m), 2.76 (3H, s), 2.66 (3H, s), 1.33 (6H, d, J=6.9 Hz).

STEP 8. 2-[4-(6-Bromo-2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 6-bromo-3-[4-(2-chloroethyl)phenyl]-2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (step 7).

MS (EI) *m/z* 412 (M⁺); ¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 3.60 (2H, t, J=6.5 Hz), 3.16-3.02 (1H, m), 3.02 (2H, t, J=6.5 Hz), 2.77 (3H, s), 2.68 (3H, s), 1.33 (6H, d, J=6.9 Hz).

STEP 9. [4-(2-Isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(6-bromo-2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 8).

H-NMR (CDCl₃) δ 7.49 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 6.93 (1H, s), 6.60 (2H, br.s), 3.32-3.00 (5H, m), 2.65 (3H, s), 2.48 (3H, s), 1.31 (6H, d, J=6.8 Hz).

STEP 10. 2-Isopropyl-5,7-dimethyl-3-(4-{2-[(4-

- 5 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-
b]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from [4-(2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 9).

- 10 ¹H-NMR (CDCl₃) δ 7.87 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=8.3 Hz), 7.23 (2H, d, J=8.4 Hz), 7.17 (2H, d, J=8.4 Hz), 6.91 (1H, s), 6.08 (1H, br.s), 3.56-3.43 (2H, m), 3.02-2.89 (1H, m), 2.85 (2H, t, J=6.3 Hz), 2.67 (3H, s), 2.41 (6H, s), 1.26 (6H, d, J=6.8 Hz).

EXAMPLE 10

- 15 2-ISOPROPYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 2-isopropyl-5,7-dimethyl-3-(4-{2-[(4-

- 20 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-
b]pyridine (Example 9).

MS (ESI) *m/z* 506 (M + H)⁺.

EXAMPLE 11

- 25 2-BUTYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3*H*-
IMIDAZO[4,5-*b*]PYRIDINE
STEP 1. 2-[4-(6-Bromo-2-butyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-

yl)phenyl]ethyl pentanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-5-bromo-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethanol (step 4 of Example 9) and pentanoyl chloride.

- 5 MS (EI) m/z 485 (M^+); 1H -NMR ($CDCl_3$) δ 7.42 (2H, d, $J=8.3$ Hz), 7.31 (2H, d, $J=8.3$ Hz), 4.37 (2H, t, $J=6.9$ Hz), 3.05 (2H, t, $J=6.9$ Hz), 2.79 (2H, t, $J=7.7$ Hz), 2.75 (3H, s), 2.67 (3H, s), 2.33 (2H, t, $J=7.5$ Hz), 1.75-1.54 (4H, m), 1.40-1.20 (4H, m), 0.91 (3H, t, $J=7.3$ Hz), 0.84 (3H, t, $J=7.3$ Hz).

STEP 2. 2-[4-(6-Bromo-2-butyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-bromo-2-butyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl pentanoate (step 1).

MS (EI) m/z 401 (M^+).

- 15 STEP 3. 6-Bromo-2-butyl-3-[4-(2-chloroethyl)phenyl]-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 7 Example 1 from 2-[4-(6-bromo-2-butyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol (step 2).

- 20 MS (EI) m/z 419 (M^+).

STEP 4. 2-[4-(6-Bromo-2-butyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 Example 1 from 6-bromo-2-butyl-3-[4-(2-chloroethyl)phenyl]-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (step 3).

- 25 MS (EI) m/z 426 (M^+); 1H -NMR ($CDCl_3$) δ 7.43 (2H, d, $J=8.4$ Hz), 7.33 (2H, d, $J=8.4$ Hz), 3.61 (2H, t, $J=7.2$ Hz), 3.01 (2H, t, $J=7.2$ Hz), 2.79 (2H, t, $J=7.9$ Hz),

2.75 (3H, s), 2.67 (3H, s), 1.75-1.60 (2H, m), 1.36-1.20 (2H, m), 0.84 (3H, t, J=7.3 Hz).

STEP 5. 2-[4-(2-Butyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine

- 5 The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(6-bromo-2-butyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 4).

¹H-NMR (CDCl₃) δ 7.59 (2H, d, J=8.3 Hz), 7.35 (2H, d, J=8.3 Hz), 6.90 (1H, s), 3.52-3.22 (4H, m), 3.01 (2H, br.s), 2.90 (2H, t, J=7.7 Hz), 2.74 (3H, s), 2.56 (3H, s), 1.79-1.62 (2H, m), 1.41-1.23 (2H, m), 0.84 (3H, t, J=7.5 Hz).

10

STEP 6. 2-Butyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step

- 15 10 of Example 1 from 2-[4-(2-butyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 5).

¹H-NMR (CDCl₃) δ 7.86 (2H, d, J=8.2 Hz), 7.31 (2H, d, J=8.2 Hz), 7.22 (2H, d, J=8.3 Hz), 7.14 (2H, d, J=8.3 Hz), 6.91 (1H, s), 6.09 (1H, br.s), 3.56-3.44 (2H, m), 2.84 (2H, t, J=6.4 Hz), 2.70-2.59 (5H, m), 2.42 (3H, s), 2.41 (3H, s), 1.69-1.43 (2H, m), 1.30-1.18 (2H, m), 0.80 (3H, t, J=7.3 Hz).

20

EXAMPLE 12

2-BUTYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, SODIUM SALT

- 25 The title compound was prepared according to the procedure described in Example 2 from 2-butyl-5,7-dimethyl-3-(4-{2-[(4-

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methylphenyl)sulfonyl]amino} carbonyl)amino]ethyl} phenyl)-3*H*-imidazo[4,5-*b*]pyridine (Example 11).

MS (ESI) *m/z* 520 (*M* + *H*)⁺.

EXAMPLE 13

- 5 2-ISOBUTYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE
STEP 1. 2-[4-(2-Isobutyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl 3-methylbutanoate
- 10 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl} ethanol (step 4 of Example 1) and isovaleryl chloride.
 MS (EI) *m/z* 407 (*M*⁺).
STEP 2. 2-[4-(2-Isobutyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol
- 15 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-isobutyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl 3-methylbutanoate (step 1).
 MS (EI) *m/z* 323 (*M*⁺).
- 20 STEP 3. 3-[4-(2-Chloroethyl)phenyl]-2-isobutyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine
 The title compound was prepared according to the procedure described in step 7 Example 1 from 2-[4-(2-isobutyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 2).
- 25 MS (EI) *m/z* 341 (*M*⁺); ¹H-NMR (CDCl₃) δ 7.41 (2H, d, *J*=8.2 Hz), 7.33 (2H, d, *J*=8.2 Hz), 6.90 (1H, s), 3.80 (2H, t, *J*=6.5 Hz), 3.18 (2H, t, *J*=6.5 Hz), 2.68 (2H,

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d, J=7.5 Hz), 2.66 (3H, s), 2.51 (3H, s), 2.14-1.96 (1H, m), 0.86 (6H, d, J=6.6 Hz).

STEP 4. 2-[4-(2-Isobutyl)-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

- 5 The title compound was prepared according to the procedure described in step 8 Example 1 from 3-[4-(2-chloroethyl)phenyl]-2-isobutyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (step 3).

MS (EI) *m/z* 348 (*M*⁺); ¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 6.91 (1H, s), 3.60 (2H, t, J=6.5 Hz), 3.00 (2H, t, J=6.5 Hz), 2.69 (2H, d, J=7.5 Hz), 2.65 (3H, s), 2.52 (3H, s), 2.08-1.98 (1H, m), 0.87 (6H, d, J=6.7 Hz).

STEP 5. 2-[4-(2-Isobutyl)-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine

- 15 The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-isobutyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 4).

¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 6.91 (1H, s), 3.09 (2H, t, J=6.4 Hz), 2.93 (2H, t, J=6.4 Hz), 2.80 (2H, br.s), 2.68 (2H, d, J=7.5 Hz), 2.66 (3H, s), 2.53 (3H, s), 2.18-2.00 (1H, m), 0.88 (6H, d, J=6.8 Hz).

- 20 STEP 6. 2-Isobutyl-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl)phenyl)-3*H*-imidazo[4,5-*b*]pyridine

- The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-isobutyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 5).

¹H-NMR (CDCl₃) δ 7.85 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 7.21 (2H, d, J=8.3 Hz), 7.12 (2H, d, J=8.3 Hz), 6.91 (1H, s), 6.14 (1H, br.s), 3.55-3.42 (2H,

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m), 2.82 (2H, t, J=6.3 Hz), 2.65 (3H, s), 2.53 (2H, d, J=7.3 Hz), 2.41 (3H, s), 2.39 (3H, s), 2.10-1.92 (1H, m), 0.81 (6H, d, J=6.6 Hz).

EXAMPLE 14

2-ISOBUTYL-5,7-DIMETHYL-3-(4-{2-[(4-

- 5 METHYLPHENYL)SULFONYL]AMINO} CARBONYL)AMINO]ETHYL}PH
ENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE, SODIUM SALT

The title compound was prepared according to the procedure described in

- Example 2 from 2-isobutyl-5,7-dimethyl-3-(4-{2-[(4-
methylphenyl)sulfonyl]amino} carbonyl)amino]ethyl}phenyl)-3H-imidazo[4,5-
10 *b*]pyridine (Example 13).

MS (ESI) m/z 520 (M + H)⁺.

EXAMPLE 15

5,7-DIMETHYL-3-(4-{2-[(4-

- 15 METHYLPHENYL)SULFONYL]AMINO} CARBONYL)AMINO]ETHYL}PH
ENYL)-2-NEOPENTYL-3H-IMIDAZO[4,5-*b*]PYRIDINE

STEP 1. 2-[4-(2-Neopentyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl
3,3-dimethylbutanoate

The title compound was prepared according to the procedure described in step 5
of Example 1 from 2-[4-(3-amino-4,6-dimethyl-2-

- 20 pyridinyl)amino]phenyl]ethanol (step 4 of Example 1) and *tert*-butylacetyl
chloride.

MS (EI) m/z 435 (M⁺).

STEP 2. 2-[4-(2-Neopentyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-
yl)phenyl]ethanol

- 25 The title compound was prepared according to the procedure described in step 6
of Example 1 from 2-[4-(2-neopentyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-
yl)phenyl]ethyl 3,3-dimethylbutanoate (step 1).

MS (EI) m/z 337 (M^+).

STEP 3. 3-[4-(2-Chloroethyl)phenyl]-2-neopentyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 7

- 5 Example 1 from 2-[4-(2-neopentyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 2).

$^1\text{H-NMR}$ (CDCl_3) δ 7.41 (2H, d, $J=8.2$ Hz), 7.30 (2H, d, $J=8.2$ Hz), 6.89 (1H, s), 3.81 (2H, t, $J=6.5$ Hz), 3.18 (2H, t, $J=6.5$ Hz), 2.79 (2H, s), 2.66 (3H, s), 2.51 (3H, s), 0.89 (9H, s).

- 10 STEP 4. 2-[4-(2-Neopentyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8

Example 1 from 3-[4-(2-chloroethyl)phenyl]-2-neopentyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (step 3).

- 15 MS (EI) m/z 362 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 7.42 (2H, d, $J=8.3$ Hz), 7.31 (2H, d, $J=8.3$ Hz), 6.91 (1H, s), 3.62 (2H, t, $J=6.5$ Hz), 3.02 (2H, t, $J=6.5$ Hz), 2.78 (2H, s), 2.68 (3H, s), 2.53 (3H, s), 0.88 (9H, s).

STEP 5. 2-[4-(2-Neopentyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine

- 20 The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-neopentyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 4).

MS (EI) m/z 336 (M^+).

STEP 6. 2-Neopentyl-5,7-dimethyl-3-(4-{2-[(4-

- 25 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine

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The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-neopentyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 5).

¹H-NMR (CDCl₃) δ 7.86 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=8.3 Hz), 7.22 (2H, d, J=8.3 Hz), 7.14 (2H, d, J=8.3 Hz), 6.91 (1H, s), 6.18 (1H, br.s), 3.56-3.46 (2H, m), 2.85 (2H, t, J=6.4 Hz), 2.65 (3H, s), 2.60 (2H, s), 2.41 (3H, s), 2.40 (3H, s), 0.87 (9H, s).

EXAMPLE 16

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-NEOPENTYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-neopentyl-3*H*-imidazo[4,5-*b*]pyridine (Example 15).

MS (ESI) *m/z* 534 (M + H)⁺.

EXAMPLE 17

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-[2-(1,3-THIAZOL-2-YL)ETHYL]-3*H*-IMIDAZO[4,5-*b*]PYRIDINE

STEP 1. *N*-[4-(2-Chloroethyl)phenyl]-*N*-(4,6-dimethyl-3-nitro-2-pyridinyl)amine

The title compound was prepared according to the procedure described in step 7 Example 1 from 2-{4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol (step 3 of Example 1).

¹H-NMR (CDCl₃) δ 9.46 (1H, br.s), 8.29 (1H, d, J=8.8 Hz), 7.42 (1H, d, J=1.7 Hz), 7.35 (2H, d, J=8.3 Hz), 7.22 (2H, d, J=8.3 Hz), 6.97 (1H, dd, J=8.8, 1.7 Hz), 3.77 (2H, t, J=7.2 Hz), 3.13 (2H, t, J=7.2 Hz).

STEP 2. *N*²-[4-(2-Chloroethyl)phenyl]-4,6-dimethyl-2,3-pyridinediamine

The title compound was prepared according to the procedure described in step 3 of Example 6 from *N*-[4-(2-chloroethyl)phenyl]-*N*-(4,6-dimethyl-3-nitro-2-pyridinyl)amine (step 1).

5 MS (EI) *m/z* 383 (*M*⁺).

STEP 3. 3-[4-(2-Chloroethyl)phenyl]-5,7-dimethyl-2-[2-(1,3-thiazol-2-yl)ethyl]-3*H*-imidazo[4,5-*b*]pyridine

- To a mixture of *N*²-[4-(2-chloroethyl)phenyl]-4,6-dimethyl-2,3-pyridinediamine (step 2, 276 mg, 1.0 mmol) and 3-(1,3-thiazol-2-yl)propanoic acid (157 mg, 1.0 mmol) in dichloromethane (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, hydrochloride (WSC) (192 mg, 1.0 mmol) in one portion. The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was suspended in toluene (20 mL) and heated at 150 °C for 5 h. The reaction
- 10 mixture was poured into water (50 mL), the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (100 mL). The combined organic phases were washed with brine (50 mL) and dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to afford
- 15 210 mg (53%) of the title compound: MS (EI) *m/z* 396 (*M*⁺); ¹H-NMR (CDCl₃) δ 7.63 (1H, d, *J*=3.4 Hz), 7.39 (2H, d, *J*=8.3 Hz), 7.28 (2H, d, *J*=8.3 Hz), 7.15 (1H, d, *J*=3.4 Hz), 6.93 (1H, s), 3.78 (2H, t, *J*=7.4 Hz), 3.69-3.50 (2H, m), 3.39-3.20 (2H, m), 3.15 (2H, t, *J*=7.4 Hz), 2.66 (3H, s), 2.53 (3H, s).
- 20 STEP 4. 2-[4-{5,7-Dimethyl-2-[2-(1,3-thiazol-2-yl)ethyl]-3*H*-imidazo[4,5-*b*]pyridin-3-yl}phenyl)ethyl azide

The title compound was prepared according to the procedure described in step 8 Example 1 from 3-[4-(2-chloroethyl)phenyl]-5,7-dimethyl-2-[2-(1,3-thiazol-2-yl)ethyl]-3*H*-imidazo[4,5-*b*]pyridine (step 3).

MS (EI) *m/z* 403 (*M*⁺); ¹H-NMR (CDCl₃) δ 7.63 (1H, d, *J*=3.5 Hz), 7.38 (2H, d, *J*=8.4 Hz), 7.28 (2H, d, *J*=8.4 Hz), 7.15 (1H, d, *J*=3.5 Hz), 6.93 (1H, s), 3.63-3.54 (4H, m), 3.34-3.26 (2H, m), 2.98 (2H, t, *J*=7.4 Hz), 2.68 (3H, s), 2.53 (3H, s).

STEP 5. 2-(4-{5,7-Dimethyl-2-[2-(1,3-thiazol-2-yl)ethyl]-3*H*-imidazo[4,5-*b*]pyridin-3-yl}phenyl)ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-(4-{5,7-dimethyl-2-[2-(1,3-thiazol-2-yl)ethyl]-3*H*-imidazo[4,5-*b*]pyridin-3-yl}phenyl)ethyl azide (step 4).

MS (EI) *m/z* 377 (*M*⁺).

STEP 6. 5,7-Dimethyl-3-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-2-[2-(1,3-thiazole-2-yl)ethyl]-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-(4-{5,7-dimethyl-2-[2-(1,3-thiazol-2-yl)ethyl]-3*H*-imidazo[4,5-*b*]pyridin-3-yl}phenyl)ethylamine (step 5).

MS (ESI) *m/z* 575 (*M* + *H*)⁺; ¹H-NMR (CDCl₃) δ 7.83 (2H, d, *J*=8.3 Hz), 7.61 (1H, d, *J*=3.5 Hz), 7.32 (2H, d, *J*=8.3 Hz), 7.19-7.15 (3H, m), 7.07 (2H, d, *J*=8.2 Hz), 6.91 (1H, s), 6.21 (1H, br.s), 3.52-3.40 (4H, m), 3.20-3.13 (2H, m), 2.81 (2H, t, *J*=6.1 Hz), 2.65 (3H, s), 2.44 (3H, s), 2.41 (3H, s).

EXAMPLE 18

3-{4-[2-[(4-BIPHENYLSULFONYL)AMINO]CARBONYL}AMINO]ETHYL}PHENYL}-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE

STEP 1. Phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylcarbamate

To a stirred solution of 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylamine (step 9 of Example 1, 1.55 g, 5.3 mmol) and triethylamine (0.80 mL, 5.8 mmol) in dichloromethane (26 mL) cooled in an ice bath was added dropwise phenyl chloroformate (0.69 mL, 5.5 mmol), and the mixture was stirred at ambient temperature. After 30 min, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate (30 mL) and dichloromethane (30 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (30 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was recrystallized from dichloromethane/hexane to give 1.90 g (87%) of the title compound as pale brown crystals: ¹H-NMR (CDCl₃) δ 7.43-7.11 (9H, m), 6.91 (1H, s), 5.50 (1H, br.s), 3.57 (2H, pseudo q, J=6.9 Hz), 2.98 (2H, t, J=6.9 Hz), 2.83 (2H, q, J=7.6 Hz), 2.66 (3H, s), 2.52 (3H, s), 1.28 (3H, t, J=7.6 Hz).

STEP 2. 3-[4-[2-({[(4-Biphenylsulfonyl)amino]carbonyl}amino)ethyl]phenyl]-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

To a stirred solution of 4-biphenylsulfonamide (Greenlee, W. J.; Walsh, T. F.; et al. *Eur. Pat. Appl.*, EP 617001 (1994)., 56 mg, 0.24 mmol) in DMF (3 mL) was added NaH (60% oil dispersion, 20 mg, 0.5 mmol) at room temperature. After 5min, phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylcarbamate (step 1, 100 mg, 0.24 mmol) was added, and the mixture was stirred for an additional 1h. The mixture was poured into water (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined extracts were washed with water (50 mL), brine (50 mL) and dried (MgSO₄). Removal of solvent gave white oily solids. Purification by preparative TLC (ethyl acetate)

gave 66 mg (50%) of the title compound as a colorless oil: MS (ESI) m/z 554 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 8.06 (2H, d, $J=8.6$ Hz), 7.13 (2H, d, $J=8.6$ Hz), 7.60-7.53 (2H, m), 7.48-7.36 (3H, m), 7.21 (2H, d, $J=8.4$ Hz), 7.12 (2H, d, $J=8.3$ Hz), 6.92 (1H, s), 6.11 (1H, br.t, $J=5.5$ Hz), 3.54 (2H, dt, $J=5.9, 6.0$ Hz), 2.89 (2H, d, $J=6.0$ Hz), 2.64 (2H, q, $J=7.5$ Hz), 2.66 (3H, s), 2.40 (3H, s), 1.18 (3H, t, $J=7.5$ Hz).

EXAMPLE 19

2-ETHYL-5,7-DIMETHYL-3-{4-[2-({[(1-NAPHTHYLSULFONYL)AMINO]CARBONYL}AMINO)ETHYL]PHENYL}-3H-IMIDAZO[4,5-*b*]PYRIDINE

The title compound was prepared according to the procedure described in step 2 of Example 18 from phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 18) and 1-naphthylsulfonamide (Arnsward, M.; Neumann, W.P. *Chem. Ber.*, 1991, 124, 1997; Khorgami, M.H. *Synthesis*, 1972, 574).

MS (ESI) m/z 528 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 8.52-8.48 (1H, m), 8.36 (1H, dd, $J=1.1, 7.3$ Hz), 8.11 (1H, d, 8.3 Hz), 8.00-7.94 (1H, m), 7.63-7.50 (3H, m), 7.20 (2H, d, $J=8.4$ Hz), 7.13 (2H, d, $J=8.4$ Hz), 6.94 (1H, s), 6.32 (1H, br.t, $J=5.7$ Hz), 3.50 (2H, dt, $J=5.9, 6.0$ Hz), 2.82 (2H, t, $J=6.2$ Hz), 2.68 (2H, q, $J=7.5$ Hz), 2.65 (3H, s), 2.41 (3H, s), 1.21 (3H, t, $J=7.5$ Hz).

EXAMPLE 20

2-ETHYL-5,7-DIMETHYL-3-{4-[2-({[(2-NAPHTHYLSULFONYL)AMINO]CARBONYL}AMINO)ETHYL]PHENYL}-3H-IMIDAZO[4,5-*b*]PYRIDINE

The title compound was prepared according to the procedure described in step 2 of Example 18 from phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-

b]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 18) and 2-naphthylsulfonamide.

MS (ESI) m/z 528 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 8.60 (1H, s), 8.01-7.84 (5H, m), 7.64-7.52 (2H, m), 7.20-7.08 (4H, m), 6.92 (1H, s), 6.20 (1H, t, J=5.6 Hz),
5 3.52-3.45 (2H, q, J=6.1 Hz), 2.84-2.80 (2H, t, J=6.3 Hz), 2.71-2.62 (2H, q, J=6.6 Hz), 2.66 (3H, s), 2.43 (3H, s), 1.22-1.16 (3H, t, J=6.6 Hz).

EXAMPLE 21

2-ETHYL-5,7-DIMETHYL-3-(4-{2-[(2-THIENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-
10 3H-IMIDAZO[4,5-b]PYRIDINE

The title compound was prepared according to the procedure described in step 2 of Example 18 from phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 18) and 2-thiophenesulfonamide (Huang, H.C.; Reinhard, E.J.; Reitz, D.B. *Tetrahedron*
15 *Lett.*, 1994, 35, 7201.; Graham, S.L.; Scholz, T.H. *Synthesis*, 1986, 1031).

¹H-NMR (CDCl₃) δ 8.01 (1H, s), 7.78 (1H, dd, J=1.3, 4.9 Hz), 7.63 (1H, dd, J=1.3, 4.9 Hz), 7.22 (2H, d, J=8.3 Hz), 7.14 (2H, d, J=8.3 Hz), 7.09 (1H, dd, J=3.8, 5.0 Hz), 6.92 (1H, s), 6.05 (1H, t, J=5.3 Hz), 3.53 (2H, q, J=6.2 Hz), 2.96 (3H, s), 2.88 (3H, s), 2.87 (2H, t, J=6.2 Hz), 2.67 (2H, q, J=7.5 Hz), 2.65 (3H, s),
20 2.43 (3H, s), 1.20 (3H, t, J=7.5 Hz).

EXAMPLE 22

3-(4-{2-[(5-CHLORO-2-THIENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-
2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE

25 The title compound was prepared according to the procedure described in step 2 of Example 18 from phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-

b]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 18) and 5-chloro-2-thiophenesulfonamide.

MS (ESI) m/z 518 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 7.99 (1H, s), 7.58-7.56 (1H, m), 7.23-7.15 (4H, m), 6.94-6.92 (1H, m), 6.04 (1H, br), 3.53-3.51 (2H, m), 2.87 (2H, m), 2.73-2.65 (2H, q, $J=7.6$ Hz), 2.65 (3H, s), 2.44 (3H, s), 1.21 (3H, t, $J=7.6$ Hz).

EXAMPLE 23

3-(4-{2-[(1-{(4,5-DICHLORO-2-THIENYL)SULFONYL}AMINO)CARBONYL]AMINO}ETHYL)PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-*b*]PYRIDINE

The title compound was prepared according to the procedure described in step 2 of Example 18 from phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 18) and 5,6-dichloro-2-thiophenesulfonamide.

MS (ESI) m/z 552 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 7.49 (1H, s), 7.27-7.14 (4H, m), 6.84 (1H, s), 3.47 (2H, br), 2.75 (2H, br), 2.69 (2H, q, $J=7.6$ Hz), 2.64 (3H, s), 2.38 (3H, s), 1.22 (3H, t, $J=7.6$ Hz).

EXAMPLE 24

3-{4-[2-[(1-(1-BENZOTHIEN-2-YLSULFONYL)AMINO)CARBONYL]AMINO]ETHYL]PHENYL}-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-*b*]PYRIDINE

The title compound was prepared according to the procedure described in step 2 of Example 18 from phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 18) and 1-benzothiophene-2-sulfonamide (Chern, J.; Leu, Y.; et al. *J. Med. Chem.*, 1997, 40, 2276.; Graham, S.L.; Shepard, K.L.; et al. *J. Med. Chem.*, 1989, 32, 2548).

mp 128.0-130.0 °C; MS (ESI) m/z 534 ($M + H$)⁺; ¹H-NMR (DMSO- d_6) δ 8.05-8.00 (3H, m), 7.50-7.42 (2H, m), 7.36 (2H, d, $J=7.4$ Hz), 7.32 (2H, d, $J=7.4$ Hz), 6.96 (1H, s), 6.61-6.56 (1H, m), 3.34-3.28 (2H, m), 2.80 (2H, t, $J=6.6$ Hz), 2.68 (2H, q, $J=7.5$ Hz), 2.54 (3H, s), 2.40 (3H, s), 1.19 (3H, t, $J=7.5$ Hz).

5 EXAMPLE 25

3-(4-{2-[(4-(2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE
CHLOROPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE

The title compound was prepared according to the procedure described in step
10 of Example 1 from 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylamine (step 9 of Example 1) and 2-chlorobenzenesulfonyl isocyanate.

MS (ESI) m/z 512 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 8.21-8.17 (1H, d, 7.7 Hz), 7.57-7.43 (3H, m), 7.32-7.22 (4H, m), 6.93 (s, 1H), 6.34 (1H, t, $J = 5.6$ Hz), 3.56-3.49 (2H, q, $J = 6.3$ Hz), 2.89-2.85 (2H, t, $J = 6.4$ Hz), 2.80-2.71 (q, 2H, $J = 7.6$ Hz), 2.67 (3H, s), 2.49 (3H, s), 1.28-1.22 (3H, t, $J = 7.6$ Hz).

15 EXAMPLE 26

2-ETHYL-5-METHYL-3-(4-{2-[(4-(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-3H-IMIDAZO[4,5-b]PYRIDINE

20 STEP 1. 2-{4-[(6-Methyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-chloro-6-methyl-3-nitropyridine (Takayama, K.; Iwata, M.; Kono, N.; et al. *Jpn. Kokai Tokkyo Koho*, JP11292877 (1999).; Ding, C.Z.; Hunt, J.T.; Kim, S.; et al. *PCT Int. Appl.*, WO 9730992 (1997)) and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 8.24 (1H, d, J=9.1 Hz), 7.28-7.33 (4H, m), 6.65 (1H, d, J=9.2 Hz), 3.89 (2H, d, J=6.4 Hz), 2.89 (2H, d, J=6.4 Hz), 2.81 (3H, s).

STEP 2. 2-{4-[(3-Amino-6-methyl-2-pyridinyl)amino]phenyl}ethanol

To a solution of 2-{4-[(6-methyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol (step 1, 4.6 g, 16.9 mmol) in methanol (100 mL) was added 10% Pd-C (300 mg). The resulting mixture was stirred for 2 h under hydrogen atmosphere. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash column chromatography eluting with hexane/ethyl acetate (gradient elution from 1:2 to 1:5) to afford 3.8 g (92%) of the title

compound as yellow solids: ¹H-NMR (CDCl₃) δ: 7.10-7.16 (4H, m), 6.91 (1H, d, J=8.4 Hz), 6.70 (1H, d, J=8.4 Hz), 6.19 (1H, s), 3.83 (2H, t, J=6.4 Hz), 2.81 (2H, t, J=6.4 Hz), 2.35 (3H, s).

STEP 3. 2-[4-(2-Ethyl-5-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-6-methyl-2-pyridinyl)amino]phenyl}ethanol (step 2) and propionyl chloride.

MS (EI) m/z 337 (M⁺).

STEP 4. 2-[4-(2-Ethyl-5-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-5-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.90 (1H, d, J=8.3 Hz), 7.43 (2H, d, J=8.2 Hz), 7.34 (2H, d, J=8.2 Hz), 7.07 (1H, d, J=8.3 Hz), 3.93 (2H, t, J=6.6 Hz), 2.97 (2H, t, J=6.6 Hz), 2.80 (2H, q, J=7.5 Hz), 2.56 (3H, s), 1.35 (3H, t, J=7.5 Hz).

STEP 5. 2-[4-(2-Ethyl-5-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl azide

A mixture of 2-[4-(2-ethyl-5-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 4, 217 mg, 0.77 mmol) in THF (20 mL) was added diethyl azodicarboxylate (DEAD) (0.3 mL, 1.5 mmol), triphenylphosphine (380 mg, 1.5 mmol) and diphenylphosphoryl azide (DPPA) (0.4 mL, 1.5 mmol). The mixture was stirred at room temperature for 4.5 h. After removal of solvent, the residue was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (gradient elution from 1:1 to 1:2) to afford 70 mg (30%) of the title compound as a brown oil: ¹H-NMR (CDCl₃) δ 7.90 (1H, d, J=8.1 Hz), 7.34-7.44 (4H, m), 7.08 (1H, d, J=8.1 Hz), 3.60 (2H, t, J=7.1 Hz), 3.00 (2H, t, J=7.1 Hz), 2.80 (2H, q, J=7.5 Hz), 2.57 (3H, s), 1.35 (3H, t, J=7.5 Hz).

STEP 6. 2-[4-(2-Ethyl-5-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-5-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 7.91 (1H, d, J=8.1 Hz), 7.42 (2H, d, J=8.3 Hz), 7.32 (2H, d, J=8.3 Hz), 7.06 (1H, d, J=8.1 Hz), 3.13 (2H, t, J=6.8 Hz), 2.95 (2H, t, J=6.8 Hz), 2.81 (2H, q, J=7.6 Hz), 2.55 (3H, s), 1.34 (3H, t, J=7.6 Hz).

STEP 7. 2-Ethyl-5-methyl-3-(4-{2-[4-(2-ethyl-5-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]sulfonyl}amino)carbonyl)aminoethylphenyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-5-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 6).

MS (ESI) *m/z* 476 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.95 (1H, d, J=8.0 Hz), 7.84 (2H, d, J=8.2 Hz), 7.32 (2H, d, J=8.2 Hz), 7.25 (2H, d, J=8.2 Hz), 7.17 (2H, d, J=8.2 Hz), 7.10 (1H, d, J=8.0 Hz), 6.17 (1H, br.s), 3.52 (2H, t, J=6.6 Hz), 2.86

(2H, t, J=6.6 Hz), 2.69 (2H, q, J=7.5 Hz), 2.49 (3H, s), 2.41 (3H, s), 1.27 (3H, t, J=7.5 Hz).

EXAMPLE 27

2-ETHYL-5-METHYL-3-(4-{2-[(4-

- 5 METHYLPHENYL)SULFONYL}AMINO}CARBONYL)AMINO}ETHYL}PH
ENYL)-3H-IMIDAZO[4,5-b]PYRIDINE, SODIUM SALT

The title compound was prepared according to the procedure described in

Example 2 from 2-ethyl-5-methyl-3-(4-{2-[(4-

methylphenyl)sulfonyl}amino}carbonyl)amino}ethyl}phenyl)-3H-imidazo[4,5-
10 b]pyridine (Example 26).

¹H-NMR (DMSO-d₆) δ 7.91 (1H, d, J=7.9 Hz), 7.61 (2H, d, J=6.8 Hz), 7.36 (4H, s), 7.11-7.15 (3H, m), 2.67-2.75 (4H, m), 2.50 (2H, br.s), 2.45 (3H, s), 2.28 (3H, s), 1.21-1.24 (3H, m).

EXAMPLE 28

2-ETHYL-5-METHOXY-3-(4-{2-[(4-

15 METHYLPHENYL)SULFONYL}AMINO}CARBONYL)AMINO}ETHYL}PH
ENYL)-3H-IMIDAZO[4,5-b]PYRIDINE

STEP 1. 2-{4-[(6-Methoxy-3-nitro-2-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 3

20 of Example 1 from 2-chloro-6-methoxy-3-nitropyridine and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 10.59 (1H, br.s), 8.38 (1H, d, J=9.2 Hz), 7.59 (2H, d, J=8.3 Hz), 7.23 (2H, d, J=8.3 Hz), 6.20 (1H, d, J=9.2 Hz), 3.94 (3H, s), 3.87 (2H, t, J=6.6 Hz), 2.87 (2H, t, J=6.6 Hz).

STEP 2. 2-{4-[(3-Amino-6-methoxy-2-pyridinyl)amino]phenyl}ethanol

25 A mixture of 2-{4-[(6-methoxy-3-nitro-2-pyridinyl)amino]phenyl}ethanol (step 1, 3.52 g, 12.17 mmol), iron powder (3.4 g, 60.84 mmol) and ammonium

chloride (325 mg, 6.08 mmol) in ethanol/water (v/v, 2:1, 90 mL) was heated at reflux temperature for 1 h. After cooling, the catalyst was removed and the filtrate was concentrated. The residue was extracted with ethyl acetate (100 mL) and washed with water. The organic layer was dried (MgSO₄), and concentrated to give 3.41 g (quant.) of the title compound as a black oil: ¹H-NMR (CDCl₃) δ 7.48 (2H, d, J=8.4 Hz), 7.14 (2H, d, J=8.4 Hz), 7.04 (1H, d, J=8.2 Hz), 6.75 (1H, br.s), 6.13 (1H, d, J=8.2 Hz), 3.87 (3H, s), 3.83 (2H, t, J=6.6 Hz), 2.81 (2H, t, J=6.6 Hz).

STEP 3. 2-[4-(2-Ethyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-6-methoxy-2-pyridinyl)amino]phenyl}ethanol (step 2) and propionyl chloride. TLC R_f = 0.50 (hexane/ethyl acetate = 2:1).

STEP 4. 2-[4-(2-Ethyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.91 (1H, d, J=8.6 Hz), 7.43 (2H, d, J=8.4 Hz), 7.35 (2H, d, J=8.4 Hz), 6.67 (1H, d, J=8.6 Hz), 3.98-3.88 (2H, m), 3.82 (3H, s), 2.99 (2H, t, J=6.4 Hz), 2.81 (2H, q, J=7.4 Hz), 1.34 (3H, t, J=7.4 Hz).

STEP 5. 2-[4-(2-Ethyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-(4-(2-ethyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl)ethanol (step 4).

TLC Rf = 0.78 (hexane/ethyl acetate = 1/1).

STEP 6. 2-[4-(2-Ethyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9

- 5 of Example 1 from 2-[4-(2-ethyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 7.92 (1H, d, J=8.6 Hz), 7.40-7.31 (4H, m), 6.67 (1H, d, J=8.6 Hz), 3.82 (3H, s), 3.13-3.10 (2H, m), 3.00-2.97 (2H, m), 2.80 (2H, q, J=7.6 Hz), 1.33 (3H, t, J=7.6 Hz).

- 10 STEP 7. 2-Ethyl-5-methoxy-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-

- 15 yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 7.95 (1H, d, J=8.7 Hz), 7.74 (2H, d, J=8.4 Hz), 7.34-7.27 (6H, m), 6.69 (1H, d, J=8.7 Hz), 6.55 (1H, m), 3.79 (3H, s), 3.60-3.53 (2H, m), 2.90 (2H, t, J=6.8 Hz), 2.77 (2H, q, J=7.4 Hz), 1.30 (3H, t, J=7.4 Hz).

EXAMPLE 29

- 20 2-ETHYL-5-METHOXY-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, SODIUM SALT

The title compound was prepared according to the procedure described in

Example 2 from 2-ethyl-5-methoxy-3-(4-{2-[(4-

- 25 methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine (Example 28).

¹H-NMR (DMSO-d₆) δ 7.94 (1H, d, J=8.4 Hz), 7.59 (2H, d, J=8.1 Hz), 7.41-7.34 (4H, m), 7.12 (2H, d, J=8.1 Hz), 6.68 (1H, d, J=8.4 Hz), 3.71 (3H, s), 3.14 (2H, m), 2.75-2.68 (4H, m), 2.27 (3H, s), 1.20 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 1597, 1518, 1489, 1425, 1389, 1261, 1130, 1086 cm⁻¹.

5 EXAMPLE 30

6-CHLORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-b]PYRIDINE

STEP 1. 2-{4-[(5-Methyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol

- 10 The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-chloro-5-methyl-3-nitropyridine and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.96 (1H, br.s), 8.32-8.31 (2H, m), 7.55 (2H, d, J=8.3Hz), 7.24 (2H, d, J=8.3 Hz), 3.85 (2H, m), 2.86 (2H, t, J=6.6 Hz), 2.32 (3H, s).

- 15 STEP 2. 2-{4-[(3-Amino-5-methyl-2-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[(5-methyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol (step 1).

- 20 ¹H-NMR (CDCl₃) δ 7.59 (1H, m), 7.08-7.00 (4H, m), 6.80 (1H, m), 3.74 (2H, t, J=6.6 Hz), 2.74 (2H, t, J=6.6 Hz), 2.19 (3H, s).

STEP 3. 2-[4-(2-Ethyl-6-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate

- The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-5-methyl-2-pyridinyl)amino]phenyl}ethanol (step 2) and propionyl chloride.

TLC R_f = 0.74 (dichloromethane/methanol = 10:1).

STEP 4. 2-[4-(2-Ethyl-6-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 8.12 (1H, s), 7.84 (1H, s), 7.44 (2H, d, J=8.1 Hz), 7.33 (2H, d, J=8.1 Hz), 3.91-3.85 (2H, m), 2.96 (2H, t, J=6.7 Hz), 2.82 (2H, q, J=7.5 Hz), 2.46 (3H, s), 1.36 (3H, t, J=7.5 Hz).

STEP 5. 2-[4-(2-Ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(2-ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 8.13 (1H, s), 7.84 (1H, s), 7.44 (2H, d, J=8.4 Hz), 7.36 (2H, d, J=8.4 Hz), 3.59 (2H, t, J=7.3 Hz), 3.00 (2H, t, J=7.3 Hz), 2.83 (2H, q, J=7.6 Hz), 2.46 (3H, s), 1.36 (3H, t, J=7.6 Hz).

STEP 4. 2-[4-(2-Ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 8.12 (1H, s), 7.84 (1H, s), 7.42 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz), 3.07 (2H, t, J=6.8 Hz), 2.91-2.78 (4H, m), 2.46 (3H, s), 1.36 (3H, t, J=7.5 Hz).

STEP 5. 2-Ethyl-6-methyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine

The reaction was carried out according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 8.04 (1H, d, J=1.8 Hz), 7.86-7.82 (3H, m), 7.33-7.21 (6H, m), 6.27 (1H, m), 3.52-3.49 (2H, m), 2.87 (2H, t, J=6.8 Hz), 2.76 (2H, q, J=7.6 Hz), 2.45 (3H, s), 2.41 (3H, s), 1.30 (3H, t, J=7.6 Hz).

EXAMPLE 31

6-CHLORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 2-ethyl-6-methyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine (Example 30).

¹H-NMR (DMSO-*d*₆) δ 8.04 (1H, m), 7.84 (1H, m), 7.60 (2H, d, J=8.1 Hz), 7.36 (4H, s), 7.12 (2H, d, J=8.1 Hz), 3.13 (2H, m), 2.78-2.71 (4H, m), 2.39 (3H, s), 2.27 (3H, s), 1.22 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 1601, 1518, 1423, 1375, 1283, 1250, 1128, 1084 cm⁻¹.

EXAMPLE 32

6-CHLORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE

STEP 1. 2-{4-[(5-Chloro-3-nitro-2-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,5-dichloro-3-nitropyridine (Marfat, A.; Robinson, R.P. *US pat. Appl.*, US 5811432 (1998).; Haessig, R.; Siegrist, U. *Eur. Pat. Appl.*, EP 483061 (1992).) and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 10.00 (1H, br.s), 8.51-8.50 (1H, m), 8.41 (1H, d, J=2.4 Hz), 7.53 (2H, d, J=8.4 Hz), 7.27 (2H, d, J=8.4 Hz), 3.88-3.87 (2H, m), 2.88 (2H, t, J=6.6 Hz).

STEP 2. 2-{4-[(3-Amino-5-chloro-2-pyridinyl)amino]phenyl} ethanol

- 5 The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[(5-chloro-3-nitro-2-pyridinyl)amino]phenyl} ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.73 (1H, d, J=2.2 Hz), 7.19-7.01 (4H, m), 6.97 (1H, d, J=2.2 Hz), 6.12 (1H, br.s), 3.81 (2H, t, J=6.4 Hz), 2.80 (2H, t, J=6.4 Hz).

- 10 STEP 3. 2-[4-(6-Chloro-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-5-chloro-2-pyridinyl)amino]phenyl} ethanol (step 2).

- 15 TLC R_f = 0.43 (hexane/ethyl acetate = 2:1).

STEP 4. 2-[4-(6-Chloro-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-chloro-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl propionate (step 3).

- 20 ¹H-NMR (CDCl₃) δ 8.23 (1H, d, J=2.1 Hz), 8.01 (1H, d, J=2.1 Hz), 7.45 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 7.09 (1H, s), 3.92 (2H, t, J=6.4 Hz), 2.95 (2H, t, J=6.4 Hz), 2.83 (2H, q, J=7.4 Hz), 1.36 (3H, t, J=7.4 Hz).

STEP 5. 2-[4-(6-Chloro-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

- 25 The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(6-chloro-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 4).

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¹H-NMR (CDCl₃) δ 8.25 (1H, d, J=2.2 Hz), 8.02 (1H, d, J=2.2 Hz), 7.46 (2H, d, J=8.3 Hz), 7.35 (2H, d, J=8.3 Hz), 3.60 (2H, t, J=7.2 Hz), 3.00 (2H, t, J=7.2 Hz), 2.84 (2H, q, J=7.5 Hz), 1.37 (3H, t, J=7.5 Hz).

STEP 6. 2-[4-(6-Chloro-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-

5 yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(6-chloro-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 5).

10 ¹H-NMR (CDCl₃) δ 8.22 (1H, d, J=2.1 Hz), 8.01 (1H, d, J=2.1 Hz), 7.45 (2H, d, J=8.2 Hz), 7.32 (2H, d, J=8.2 Hz), 3.13-3.08 (2H, m), 2.95-2.78 (4H, m), 1.36 (3H, t, J=7.6 Hz).

STEP 7. 6-Chloro-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine

15 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(6-chloro-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 6).

20 ¹H-NMR (CDCl₃) δ 8.20 (1H, d, J=2.2 Hz), 8.03 (1H, d, J=2.2 Hz), 7.77 (2H, d, J=8.1 Hz), 7.38-7.27 (6H, m), 6.51-6.48 (1H, m), 3.57-3.50 (2H, m), 2.90 (2H, t, J=6.8 Hz), 2.81 (2H, t, J=7.5 Hz), 1.34 (3H, t, J=7.5 Hz).

EXAMPLE 33

6-CHLORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, SODIUM SALT

25 The title compound was prepared according to the procedure described in Example 2 from 6-chloro-2-ethyl-3-(4-{2-[(4-

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methylphenyl)sulfonyl]amino}carbonyl]amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine (Example 32).

¹H-NMR (DMSO-*d*₆) δ 8.24-8.21 (2H, m), 7.60 (2H, d, *J*=8.1 Hz), 7.42-7.34 (4H, m), 7.12 (2H, d, *J*=8.1 Hz), 3.13 (2H, m), 2.81-2.69 (4H, m), 2.27 (3H, s), 1.24 (3H, t, *J*=7.4 Hz); IR (KBr) ν_{max} 1597, 1516, 1421, 1375, 1246, 1128, 1084 cm^{-1} .

EXAMPLE 34

2-ETHYL-5,6-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE

STEP 1. 2-{4-[(5,6-Dimethyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol

A mixture of 2-chloro-5,6-dimethyl-3-nitropyridine (Godard, A.; Rocca, P.; Pomel, V.; et al. *J. Organomet. Chem.*, 1996, 517, 25.; Rocca, P.; Marsais, F.; Godard, A.; et al. *Tetrahedron Lett.*, 1993, 34, 2937., 3.3 g, 17.5 mmol), 4-aminophenylethyl alcohol (3.6 g, 26.3 mmol) and 2,6-lutidine (3.7 mL) in toluene (80 mL) was stirred under reflux temperature for 19 h. The mixture was diluted with ethyl acetate (100 mL) and washed with 1N aqueous NaOH (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), and concentrated.

Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to afford 1.8 g (37%) of the title compound as orange solids: ¹H-NMR (CDCl_3) δ 8.24 (1H, br.s), 7.68 (2H, d, *J*=8.6 Hz), 7.24 (2H, d, *J*=8.6 Hz), 3.88 (2H, dt, *J*=6.1, 7.6 Hz), 2.88 (2H, t, *J*=7.6 Hz), 2.49 (3H, s), 2.26 (3H, s), 1.43 (1H, t, *J*=6.1 Hz).

STEP 2. 2-{4-[(3-Amino-5,6-dimethyl-2-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[(5,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol (step 1).

¹H-NMR (CDCl₃) δ 6.97 (2H, d, J=8.4 Hz), 6.92 (2H, d, J=8.4 Hz), 6.71 (1H, s), 6.22 (1H, br s), 3.67 (2H, t, J=6.8 Hz), 2.68 (2H, t, J=6.8 Hz), 2.29 (3H, s), 2.12 (3H, s).

STEP 3 2-[4-(2-Ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl

5 propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-5,6-dimethyl-2-pyridinyl)amino]phenyl} ethanol (step 2) and propionyl chloride.

10 ¹H-NMR (CDCl₃) δ 7.75 (1H, br.s), 7.42 (2H, d, J=8.6 Hz), 7.34 (2H, d, J=8.6 Hz), 4.37 (2H, t, J=6.6 Hz), 3.05 (2H, t, J=6.6 Hz), 2.80 (2H, q, J=7.6 Hz), 2.49 (3H, s), 2.38 (3H, s), 2.37-2.28 (2H, m), 1.34 (3H, t, J=7.6 Hz), 1.18 (3H, t, J=7.5 Hz).

STEP 4. 2-[4-(2-Ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol

15 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate (step 3).

MS (ESI) m/z 296 (M + H)⁺; ¹H-NMR (CDCl₃) δ: 7.75 (1H, br.s), 7.43 (2H, d, J=8.6 Hz), 7.33 (2H, d, J=8.6 Hz), 3.92 (2H, br.t, J=6.6 Hz), 2.97 (2H, t, J=6.6 Hz), 2.80 (2H, q, J=7.6 Hz), 2.49 (3H, s), 2.38 (3H, s), 1.34 (3H, t, J=7.6 Hz).

STEP 5. 3-[4-(2-Chloroethyl)phenyl]-2-ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridine

25 The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 7.75 (1H, br.s), 7.43 (2H, d, J=8.6 Hz), 7.36 (2H, d, J=8.6 Hz), 3.80 (2H, t, J=7.3 Hz), 3.18 (2H, t, J=7.3 Hz), 2.81 (2H, q, J=7.6 Hz), 2.50 (3H, s), 2.38 (3H, s), 1.34 (3H, t, J=7.6 Hz).

STEP 6. 2-[4-(2-Ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl

5 azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[4-(2-chloroethyl)phenyl]-2-ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridine (step 5).

10 ¹H-NMR (CDCl₃) δ 7.75 (1H, br.s), 7.42 (2H, d, J=8.4 Hz), 7.36 (2H, d, J=8.4 Hz), 3.60 (2H, t, J=7.3 Hz), 3.00 (2H, t, J=7.3 Hz), 2.80 (2H, q, J=7.6 Hz), 2.49 (3H, s), 2.38 (3H, s), 1.34 (3H, t, J=7.6 Hz).

STEP 7. 2-[4-(2-Ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylamine

15 The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl azide (step 6).

¹H-NMR (CDCl₃) δ 7.76 (1H, br.s), 7.41 (2H, d, J=7.9 Hz), 7.33 (2H, d, J=7.9 Hz), 3.12 (2H, t, J=6.9 Hz), 2.95 (2H, t, J=6.9 Hz), 2.79 (2H, q, J=6.9 Hz), 2.47 (3H, s), 2.37 (3H, s), 1.33 (3H, t, J=6.9 Hz).

20 STEP 8. 2-Ethyl-5,6-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3H-imidazo[4,5-b]pyridine

25 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylamine (step 7).

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MS (ESI) m/z 492 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 7.87 (2H, d, J=8.2 Hz), 7.79 (1H, s), 7.31 (2H, d, J=8.2 Hz), 7.23 (2H, d, J=8.1 Hz), 7.15 (2H, d, J=8.1 Hz), 6.24 (1H, m), 3.51 (2H, m), 2.85 (2H, t, J=6.1 Hz), 2.66 (2H, q, J=7.4 Hz), 2.39 (3H, s), 2.38 (3H, s), 2.36 (3H, s), 1.25 (3H, t, J=7.4 Hz).

5 EXAMPLE 35

2-ETHYL-5,6-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE, SODIUM SALT

The title compound was prepared according to the procedure described in

10 Example 2 from 2-ethyl-5,6-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3H-imidazo[4,5-*b*]pyridine (Example 34).

mp 156.0-158.5 °C; ¹H-NMR (DMSO-*d*₆) δ 7.58 (1H, s), 7.48 (2H, d, J=8.1 Hz), 7.19-7.13 (4H, m), 6.98 (2H, d, J=8.1 Hz), 6.01 (1H, br.s), 3.15-2.98 (2H, m),
15 2.59-2.55 (2H, m), 2.50 (2H, q, J=7.6 Hz), 2.19 (3H, s), 2.13 (3H, s), 2.09 (3H, s), 1.01 (3H, t, J=7.6 Hz).

EXAMPLE 36

2-[4-(2-ETHYL-5,6-DIMETHYL-3H-IMIDAZO[4,5-*b*]PYRIDIN-3-YL)PHENYL]ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

20 The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-ethyl-5,6-dimethyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 4 of Example 34).

MS (ESI) m/z 493 ($M + H$)⁺; ¹H-NMR (DMSO-*d*₆) δ 7.94 (2H, d, J=8.4 Hz), 7.78 (1H, s), 7.33 (2H, d, J=8.1 Hz), 7.25-7.16 (4H, m), 4.35 (2H, t, J=6.6 Hz),
25 2.93 (2H, t, J=6.6 Hz), 2.73 (2H, q, J=7.4 Hz), 2.46 (3H, s), 2.43 (3H, s), 2.39 (3H, s), 1.28 (3H, t, J=7.4 Hz).

EXAMPLE 37

5,6-DICHLORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-b]PYRIDINE
STEP 1. 2-[4-[(5,6-Dichloro-3-nitro-2-pyridinyl)amino]phenyl]ethanol

- 5 The title compound was prepared according to the procedure described in step 1 of Example 34 from 3-nitro-2,5,6-trichloropyridine (Horn, U.; Mutterer, F.; Weis, C.D. *Helv. Chim. Acta.*, 1976, 59,190.) and 4-aminophenylethyl alcohol. MS (EI) m/z 327 (M⁺); ¹H-NMR (CDCl₃) δ 10.11 (1H, br.s), 8.58 (1H, s), 7.57 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 3.93-3.86 (2H, m), 2.89 (2H, t, J=6.6 Hz).

STEP 2. 2-[4-[(3-Amino-5,6-dichloro-2-pyridinyl)amino]phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[4-[(5,6-dichloro-3-nitro-2-pyridinyl)amino]phenyl]ethanol (step 1).

- 15 MS (EI) m/z 297 (M⁺).

STEP 3 2-[4-(2-Ethyl-5,6-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-[(3-amino-5,6-dichloro-2-

- 20 pyridinyl)amino]phenyl]ethanol (step 2) and propionyl chloride. TLC Rf = 0.63 (ethyl acetate/hexane = 1:1).

STEP 4. 2-[4-(2-Ethyl-5,6-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-Ethyl-5,6-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate (step 3).

MS (EI) m/z 335 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 8.11 (1H, s), 7.46 (2H, d, $J=8.1$ Hz), 7.32 (2H, d, $J=8.1$ Hz), 3.97 (2H, t, $J=6.2$ Hz), 2.99 (2H, t, $J=6.2$ Hz), 2.82 (2H, q, $J=7.5$ Hz), 1.36 (3H, t, $J=7.5$ Hz).

STEP 5. 3-[4-(2-Chloroethyl)phenyl]-2-ethyl-5,6-dichloro-3H-imidazo[4,5-

5 b]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-5,6-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol (step 4).

10 $^1\text{H-NMR}$ (CDCl_3) δ 8.13 (1H, s), 7.45 (2H, d, $J=8.1$ Hz), 7.33 (2H, d, $J=8.1$ Hz), 3.80 (2H, t, $J=7.2$ Hz), 3.19 (2H, t, $J=7.2$ Hz), 2.82 (2H, q, $J=7.5$ Hz), 1.36 (3H, t, $J=7.5$ Hz).

STEP 6. 2-[4-(2-Ethyl-5,6-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl azide

15 The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[4-(2-chloroethyl)phenyl]-2-ethyl-5,6-dichloro-3H-imidazo[4,5-b]pyridine (step 5).

MS (EI) m/z 360 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 8.11 (1H, s), 7.44 (2H, d, $J=8.4$ Hz), 7.33 (2H, d, $J=8.4$ Hz), 3.61 (2H, t, $J=7.2$ Hz), 3.00 (2H, t, $J=7.2$ Hz), 2.81 (2H, q, $J=7.5$ Hz), 1.35 (3H, t, $J=7.5$ Hz).

20 STEP 7. 2-[4-(2-Ethyl-5,6-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylamine

To a solution of 2-[4-(2-ethyl-5,6-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl azide (step 6, 69 mg, 0.2 mmol) in methanol (10 mL) was added Lindlar catalyst (5 mg). The resulting mixture was stirred for 6 h under
25 hydrogen atmosphere. The mixture was filtered through a pad of Celite and the filtrate was concentrated. Purification by preparative TLC (dichloromethane/methanol = 10:1) gave 60 mg (94%) of the title compound as

colorless solids: MS (EI) m/z 334 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 8.11 (1H, s), 7.43 (2H, d, $J=8.3$ Hz), 7.30 (2H, d, $J=8.3$ Hz), 3.11 (2H, t, $J=6.6$ Hz), 2.92 (2H, t, $J=6.6$ Hz), 2.81 (2H, q, $J=7.5$ Hz), 1.35 (3H, t, $J=7.5$ Hz).

STEP 8. 5,6-Dichloro-2-ethyl-3-(4-{2-[(4-

- 5 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3H-imidazo[4,5-
b]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-5,6-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylamine (step 7).

- 10 mp 188.0-189.0 °C; MS (ESI) m/z 532 ($M + H^+$); $^1\text{H-NMR}$ (CDCl_3) δ 8.12 (1H, s), 7.77 (2H, d, $J=8.4$ Hz), 7.36-7.25 (6H, m), 6.49 (1H, br.t, $J=5.9$ Hz), 3.54 (2H, dt, $J=5.9$, 7.0 Hz), 2.90 (2H, t, $J=7.0$ Hz), 2.78 (2H, q, $J=7.5$ Hz), 2.41 (3H, s), 1.33 (3H, t, $J=7.5$ Hz).

EXAMPLE 38

- 15 5-CHLORO-2-ETHYL-6-METHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-3H-IMIDAZO[4,5-b]PYRIDINE

STEP 1. 2-{4-[(6-Chloro-5-methyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol

- 20 The title compound was prepared according to the procedure described in step 1 of Example 34 from 2,6-dichloro-5-methyl-3-nitropyridine (Horn, U.; Mutterer, F.; Weis, C.D. *Helv. Chim. Acta.*, 1976, 59,190.) and 4-aminophenylethyl alcohol.

$^1\text{H-NMR}$ (CDCl_3) δ 10.05 (1H, br.s), 8.34 (1H, s), 7.57 (2H, d, $J=7.7$ Hz), 7.24 (2H, d, $J=7.7$ Hz), 3.86 (2H, t, $J=5.9$ Hz), 2.87 (2H, t, $J=5.9$ Hz), 2.33 (3H, s).

- 25 STEP 2. 2-{4-[(3-Amino-6-chloro-5-methyl-2-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[(6-chloro-5-methyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.14-7.08 (4H, m), 6.86 (1H, s), 6.21 (1H, br.s), 3.79 (2H, t, J=6.4 Hz), 2.78 (2H, t, J=6.4 Hz), 2.33 (3H, s).

STEP 3. 2-[4-(5-Chloro-2-ethyl-6-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-6-chloro-5-methyl-2-pyridinyl)amino]phenyl}ethanol (step 2) and propionyl chloride.

MS (EI) m/z 371 (M⁺).

STEP 4. 2-[4-(5-Chloro-2-ethyl-6-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5-chloro-2-ethyl-6-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate (step 3).

MS (EI) m/z 315 (M⁺); ¹H-NMR (CDCl₃) δ 7.87 (1H, s), 7.42 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 3.92 (2H, t, J=6.6 Hz), 2.96 (2H, t, J=6.6 Hz), 2.79 (2H, q, J=7.7 Hz), 2.47 (3H, s), 1.34 (3H, t, J=7.7 Hz).

STEP 5. 3-[4-(2-Chloroethyl)phenyl]-5-chloro-2-ethyl-5-methyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(5-chloro-2-ethyl-6-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol (step 4).

MS (EI) m/z 333 (M⁺); ¹H-NMR (CDCl₃) δ 7.88 (1H, s), 7.42 (2H, d, J=8.3 Hz), 7.33 (2H, d, J=8.3 Hz), 3.79 (2H, t, J=7.3 Hz), 3.17 (2H, t, J=7.3 Hz), 2.80 (2H, q, J=7.0 Hz), 2.48 (3H, s), 1.35 (3H, t, J=7.0 Hz).

STEP 6. 2-[4-(5-Chloro-2-ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[4-(2-chloroethyl)phenyl]-5-chloro-2-ethyl-5-methyl-3*H*-imidazo[4,5-*b*]pyridine (step 5).

¹H-NMR (CDCl₃) δ 7.87 (1H, s), 7.42 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.4 Hz), 3.59 (2H, t, J=7.1 Hz), 2.98 (2H, t, J=7.1 Hz), 2.81 (2H, q, J=7.6 Hz), 2.48 (3H, s), 1.35 (3H, t, J=7.6 Hz).

STEP 7. 2-[4-(5-Chloro-2-ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine.

The title compound was prepared according to the procedure described in step 7 of Example 37 from 2-[4-(5-chloro-2-ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 6).

¹H-NMR (CDCl₃) δ 7.88 (1H, s), 7.40 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=8.3 Hz), 3.07 (2H, t, J=6.8 Hz), 2.87 (2H, t, J=6.8 Hz), 2.80 (2H, q, J=7.3 Hz), 2.48 (3H, s), 1.34 (3H, t, J=7.3 Hz).

STEP 8. 5-Chloro-2-ethyl-6-methyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl]phenyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(5-chloro-2-ethyl-6-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 7).

mp 205-206 °C; MS (ESI) m/z 512 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.90 (1H, s), 7.79 (2H, d, J=8.3 Hz), 7.33-7.23 (6H, m), 6.46 (1H, br.s), 3.55-3.49 (2H, m), 2.88 (2H, t, J=6.8 Hz), 2.76 (2H, q, J=7.6 Hz), 2.48 (3H, s), 2.41 (3H, s), 1.31 (3H, t, J=7.6 Hz).

EXAMPLE 39

5-CHLORO-2-ETHYL-7-METHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-b]PYRIDINE

STEP 1. 2-{4-[(6-Chloro-4-methyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol

- 5 The title compound was prepared according to the procedure described in step 1 of Example 34 from 2,6-dichloro-4-methyl-3-nitropyridine (Inubushi, A.; Kawano, E.; Shimada, Ke.; et al. *PCT Int. Appl.*, WO 9802442 (1998)) and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ: 9.56 (1H, s), 7.49 (2H, d, J=8.4 Hz), 7.22 (2H, d, J=8.4 Hz), 6.64 (1H, s), 3.84 (2H, t, J=6.4 Hz), 2.84 (2H, t, J=6.4 Hz), 2.55 (3H, s).

10 STEP 2. 2-{4-[(3-Amino-6-chloro-4-methyl-2-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[(6-chloro-4-methyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol (step 1).

- 15 MS (EI) m/z 277 (M⁺).

STEP 3. 2-[4-(5-Chloro-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate

- The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-6-chloro-4-methyl-2-pyridinyl)amino]phenyl}ethanol (step 2).

TLC Rf = 0.46 (ethyl acetate/hexane = 1:1).

20 STEP 4. 2-[4-(5-Chloro-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanol

- The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5-chloro-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate (step 3).

MS (EI) m/z 315 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 7.43 (2H, d, $J=8.4$ Hz), 7.31 (2H, d, $J=8.4$ Hz), 7.07 (1H, s), 4.00-3.85 (2H, m), 2.97 (2H, t, $J=6.6$ Hz), 2.83 (2H, q, $J=7.5$ Hz), 2.68 (3H, s), 1.30 (3H, t, $J=7.5$ Hz).

STEP 5. 3-[4-(2-Chloroethyl)phenyl]-5-chloro-2-ethyl-7-methyl-3H-

5 imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(5-chloro-2-ethyl-7-methyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 4).

$^1\text{H-NMR}$ (CDCl_3) δ 7.42 (2H, d, $J=8.1$ Hz), 7.33 (2H, d, $J=8.1$ Hz), 7.07 (1H, s), 3.79 (2H, t, $J=7.3$ Hz), 3.17 (2H, t, $J=7.3$ Hz), 2.83 (2H, q, $J=7.5$ Hz), 2.68 (3H, s), 1.30 (3H, t, $J=7.5$ Hz).

STEP 6. 2-[4-(5-Chloro-2-ethyl-7-methyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[4-(2-chloroethyl)phenyl]-5-chloro-2-ethyl-7-methyl-3H-imidazo[4,5-*b*]pyridine (step 5).

$^1\text{H-NMR}$ (CDCl_3) δ 7.42 (2H, d, $J=8.6$ Hz), 7.33 (2H, d, $J=8.6$ Hz), 7.07 (1H, s), 3.56 (2H, t, $J=7.2$ Hz), 2.99 (2H, t, $J=7.2$ Hz), 2.83 (2H, q, $J=7.5$ Hz), 2.68 (3H, s), 1.29 (3H, t, $J=7.5$ Hz).

20 STEP 7. 2-[4-(5-Chloro-2-ethyl-7-methyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine.

To a stirred solution of 2-[4-(5-chloro-2-ethyl-7-methyl-3H-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 6, 57 mg, 0.2 mmol) in THF (5 mL) was added triphenylphosphine (47 mg, 0.2 mmol) at room temperature. After completion of the addition, the stirring was continued for an additional 3 h at the same temperature. To the resulting mixture was added water (0.1 mL) at room temperature, and the reaction mixture was stirred at room temperature for 20 h.

The mixture was concentrated to give colorless solids. Purification by preparative TLC (dichloromethane/methanol/triethylamine = 10:1:1) gave 13 mg (25%) of the title compound as colorless solids: MS (EI) m/z 313 (M^+).

STEP 8. 5-Chloro-2-ethyl-7-methyl-3-(4-{2-[(4-

- 5 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3H-imidazo[4,5-
b]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(5-chloro-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylamine (step 7).

- 10 MS (ESI) m/z 512 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ : 7.80 (2H, d, J=8.4 Hz), 7.34-7.23 (6H, m), 7.09 (1H, s), 6.37 (1H, br s), 3.56-3.52 (2H, m), 2.88 (2H, t, J=6.8 Hz), 2.77 (2H, q, J=7.5 Hz), 2.69 (3H, s), 2.42 (3H, s), 1.26 (3H, t, J=7.5 Hz).

EXAMPLE 40

2-ETHYL-7-METHYL-3-(4-{2-[(4-

- 15 METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-6-[(METHYLSULFONYL)AMINO]-3H-IMIDAZO[4,5-b]PYRIDINE

STEP 1.2-{4-[(4-Methyl-3,5-dinitro-2-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-chloro-4-methyl-3,5-dinitropyridine. (Czuba, *Rocz.Chem.*, 1967, 41, 479) and 4-aminophenylethyl alcohol.

- 20 ¹H-NMR (CDCl₃) δ 8.90 (1H, s), 8.50 (1H, br.s), 7.40 (2H, d, J=8.4 Hz), 7.23 (2H, d, J=8.4 Hz), 3.82 (2H, t, J=6.6 Hz), 2.84 (2H, t, J=6.6 Hz), 2.62 (3H, s).

STEP 2. 2-{4-[(3-Amino-4-methyl-5-nitro-2-pyridinyl)amino]phenyl}ethanol

To a stirred solution of 2-{4-[(4-methyl-3,5-dinitro-2-

- 25 pyridinyl)amino]phenyl}ethanol (step 1, 4.2 g, 13.1 mmol), triethylamine (9.6 mL, 68.9 mmol), 10% Pd-C (624 mg, 0.59 mmol) in acetonitrile (14 mL) was added dropwise a solution of formic acid (2.3 mL, 61.0 mmol) in acetonitrile

(6.2 mL) at 0°C over a period of 30 min. After stirring at room temperature for 5 h, the mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was dissolved in dichloromethane (100 mL). The solution was washed with 1N aqueous NaOH (50 mL), brine (50 mL), dried

- 5 (MgSO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (gradient elution from 1:1 to 1:2) afforded 2.2 g (60 %) of the title compound as red crystals: ¹H-NMR (CDCl₃) δ 8.42 (1H, s), 7.42 (2H, d, J=8.4 Hz), 7.21 (2H, d, J=8.4 Hz), 6.7 (1H, br s), 3.85 (2H, t, J=6.4 Hz), 2.86 (2H, t, J=6.6 Hz), 2.47 (3H, s).

10 STEP 3. 2-[4-(2-Ethyl-7-methyl-6-nitro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(3-amino-4-methyl-5-nitro-2-pyridinyl)amino]phenyl}ethanol (step 2) and propionyl chloride.

- 15 ¹H-NMR (CDCl₃) δ 9.03 (1H, s), 7.48 (2H, d, J=8.6 Hz), 7.33 (2H, d, J=8.4 Hz), 4.38 (2H, t, J=6.9 Hz), 3.07 (2H, t, J=6.9 Hz), 3.03 (3H, s), 2.87 (2H, q, J=7.6 Hz), 2.35 (2H, q, J=7.6 Hz), 1.35 (3H, t, J=7.4 Hz), 1.13 (3H, t, J=7.4 Hz).

STEP 4. 2-[4-(6-Amino-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate

- 20 A suspension of 2-[4-(2-ethyl-7-methyl-6-nitro-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate (step 3, 2.5 g, 6.6 mmol), 10% Pd-C (250 mg, 0.23 mmol) in methanol (100 mL) was stirred under hydrogen atmosphere for 2 h. The suspension was filtered through a pad of Celite, and the filtrate was concentrated to afford 2.4 g (99%) of the title compound as a brown oil: ¹H-
- 25 NMR (CDCl₃) δ 7.82 (1H, s), 7.41 (2H, d, J=8.2 Hz), 7.32 (2H, d, J=8.4 Hz), 4.35 (2H, t, J=7.0 Hz), 3.51 (2H, br.s), 3.03 (2H, t, J=7.0 Hz), 2.82 (2H, q, J=7.5

H₂), 2.53 (3H, s), 2.35 (2H, q, J=7.5 Hz), 1.29 (3H, t, J=7.5 Hz), 1.44 (3H, t, J=7.5 Hz).

STEP 5. 2-(4-{2-Ethyl-7-methyl-6-[(methylsulfonyl)amino]-3H-imidazo[4,5-b]pyridin-3-yl}phenyl)ethyl propionate

- 5 To a stirred solution of 2-[4-(6-amino-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate (step 4, 1.0 g, 3.0 mmol) and pyridine (280 mg, 3.5 mmol) in dichloromethane (18 mL) was added methanesulfonyl chloride (372 mg, 3.3 mmol) at 0°C, and the mixture was stirred at room temperature for 16h. The reaction was quenched with water (10 mL), and the
- 10 mixture was extracted with dichloromethane (50 mL). The organic layer was washed with brine (50 mL), dried (MgSO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with ethyl acetate (gradient elution from 1:1 to 1:2) afforded 890 mg (70 %) of the title compound as an amber oil: ¹H-NMR (CDCl₃) δ 8.26 (1H, s), 7.43 (2H, d, J=8.4 Hz), 7.32 (2H, d, J=8.2 Hz), 7.00 (1H, br.s), 4.35 (2H, t, J=7.0 Hz), 3.03-3.01 (5H, m), 2.85 (2H, q, J=7.5 Hz), 2.75 (3H, s), 2.35 (2H, q, J=7.5 Hz), 1.30 (3H, t, J=7.5 Hz), 1.14 (3H, t, J=7.5 Hz).
- 15

STEP 6. N-{2-Ethyl-3-[4-(2-hydroxyethyl)phenyl]-7-methyl-3H-imidazo[4,5-b]pyridin-6-yl}methanesulfonamide

- 20 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-(4-{2-ethyl-7-methyl-6-[(methylsulfonyl)amino]-3H-imidazo[4,5-b]pyridin-3-yl}phenyl)ethyl propionate (step 5).
- ¹H-NMR (CDCl₃) δ 8.22 (1H, s), 7.46 (2H, d, J=8.2 Hz), 7.31 (2H, d, J=8.4 Hz), 6.52 (1H, br.s), 3.93 (2H, t, J=6.6 Hz), 3.03 (3H, s), 2.97 (2H, t, J=6.6 Hz), 2.85 (2H, q, J=7.6 Hz), 2.76 (3H, s), 1.32 (3H, t, J=7.4 Hz).
- 25

STEP 7. N-{3-[4-(2-Chloroethyl)phenyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridin-6-yl}methanesulfonamide

The title compound was prepared according to the procedure described in step 7 of Example 1 from *N*-{2-ethyl-3-[4-(2-hydroxyethyl)phenyl]-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl}methanesulfonamide (step 6).

TLC Rf = 0.40 (ethyl acetate).

- 5 STEP 8. *N*-{3-[4-(2-Azidoethyl)phenyl]-2-ethyl-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl}methanesulfonamide

The title compound was prepared according to the procedure described in step 8 of Example 1 from *N*-{3-[4-(2-chloroethyl)phenyl]-2-ethyl-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl}methanesulfonamide (step 7).

- 10 ¹H-NMR (CDCl₃) δ 8.26 (1H, s), 7.44 (2H, d, J=8.1 Hz), 7.34 (2H, d, J=8.1 Hz), 6.65 (1H, br.s), 3.59 (2H, t, J=7.0 Hz), 3.03 (3H, s), 2.99 (2H, t, J=7.1 Hz), 2.86 (2H, q, J=7.4 Hz), 2.75 (3H, s), 1.31 (3H, t, J=7.5 Hz).

STEP 9. *N*-{3-[4-(2-Aminoethyl)phenyl]-2-ethyl-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl}methanesulfonamide

- 15 The title compound was prepared according to the procedure described in step 9 of Example 1 from *N*-{3-[4-(2-azidoethyl)phenyl]-2-ethyl-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl}methanesulfonamide (step 8).

TLC Rf = 0.05 (ethyl acetate).

STEP 10. 2-Ethyl-7-methyl-3-(4-{2-[(4-

- 20 methylphenyl)sulfonyl}amino}carbonyl}amino)ethyl}phenyl)-6-[(methylsulfonyl)amino]-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from *N*-{3-[4-(2-aminoethyl)phenyl]-2-ethyl-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl}methanesulfonamide (step 9).

- 25 mp 166 °C; MS (ESI) *m/z* 571.25 (M + H)⁺; ¹H-NMR (CDCl₃) δ 8.16 (1H, s), 7.81 (2H, d, J=8.1 Hz), 7.31-7.18 (6H, m), 6.39 (1H, br.s), 3.48-3.46 (2H, m), 3.00 (3H, s), 2.82-2.71 (7H, m), 2.39 (3H, s), 1.26 (3H, t, J=7.2 Hz).

EXAMPLE 416-CYANO-2-ETHYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-b]PYRIDINE5 STEP 1. 6-Hydroxy-2,4-dimethylnicotinonitrile

To a stirred solution of 6-amino-2,4-dimethylnicotinonitrile (Sato, K.; et al. *Bull.Chem.Soc.Jpn.*, 1969, 42, 2319., 22.4 g, 152 mmol) in 5% aqueous sulfuric acid (600 mL) was added dropwise a solution of sodium nitrite (25.2 g, 365 mmol) in water (100 mL) at 0°C, and the mixture was stirred at room temperature for 16 h. The resulting precipitate was collected by filtration to afford 10.2 g (45%) of the title compound: ¹H-NMR (DMSO-d₆) δ 12.27 (1H, br.s), 6.17 (1H, s), 2.38 (3H, s), 2.20 (3H, s).

10 STEP 2. 6-Hydroxy-2,4-dimethyl-5-nitronicotinonitrile

To a stirring mixture of nitric acid (fuming, 36 mL) and sulfuric acid (18 mL) was added 6-hydroxy-2,4-dimethylnicotinonitrile (step 1, 9.0 g, 60.8 mmol) in one portion, and the mixture was stirred at room temperature. After 1h, the mixture was poured in water (100 mL) and neutralized with 2N aqueous NaOH. The resulting precipitates were collected by filtration to afford 3.2g (27%) of the title compound: ¹H-NMR (DMSO-d₆) δ 2.28 (3H, s), 2.11 (3H, s).

15 STEP 3. 6-Chloro-2,4-dimethyl-5-nitronicotinonitrile

A mixture of 6-hydroxy-2,4-dimethyl-5-nitronicotinonitrile (step 2, 3.2 g, 16.6 mmol) and phosphorus oxychloride (20 mL) was stirred at 100°C for 16h. After cooling, the mixture was poured in water (100 mL). The resulting mixture was extracted with dichloromethane (3 x 100 mL). The organic layer was washed with brine (50 mL), dried (MgSO₄), and concentrated to afford 2.3g (66%) of the title compound as brown solids: ¹H-NMR (DMSO-d₆) δ 2.82 (3H, s), 2.52 (3H, s).

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STEP 4. 6-[4-(2-Hydroxyethyl)anilino]-2,4-dimethyl-5-nitronicotinonitrile

The title compound was prepared according to the procedure described in step 3 of Example 1 from 6-chloro-2,4-dimethyl-5-nitronicotinonitrile (step 3) and 4-aminophenylethyl alcohol.

- 5 ¹H-NMR (CDCl₃) δ 9.37 (1H, br.s), 7.51 (2H, d, J=8.4 Hz), 7.26 (2H, d, J=8.4 Hz), 3.89-3.87 (2H, m), 2.89 (2H, t, J=6.4 Hz), 2.72 (3H, s), 2.65 (3H, s), 1.46 (1H, t, J=5.8 Hz).

STEP 5. 5-Amino-6-[4-(2-hydroxyethyl)anilino]-2,4-dimethylnicotinonitrile

10 The title compound was prepared according to the procedure described in step 4 of Example 1 from 6-[4-(2-hydroxyethyl)anilino]-2,4-dimethyl-5-nitronicotinonitrile (step 4).

¹H-NMR (CDCl₃) δ 7.49 (2H, d, J=8.6 Hz), 7.19 (2H, d, J=8.4 Hz), 6.98 (1H, br.s), 3.89-3.82 (2H, m), 3.11 (2H, br.s), 2.85 (2H, t, J=6.6 Hz), 2.58 (3H, s), 2.38 (3H, s), 1.44 (1H, t, J=5.6 Hz).

- 15 STEP 6. 2-[4-(6-Cyano-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 5-amino-6-[4-(2-hydroxyethyl)anilino]-2,4-dimethylnicotinonitrile (step 5) and propionyl chloride.

- 20 TLC Rf = 0.4 (hexane/ethyl acetate = 1:1).

STEP 7. 2-Ethyl-3-[4-(2-hydroxyethyl)phenyl]-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-6-carbonitrile

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-cyano-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-

- 25 b]pyridin-3-yl)phenyl]ethyl propionate (step 6).

¹H-NMR (CDCl₃) δ 7.46 (2H, d, J=8.2 Hz), 7.31 (2H, d, J=8.2 Hz), 4.01-3.94 (2H, m), 3.49-3.47 (1H, m), 3.00 (2H, t, J=6.3 Hz), 2.86 (3H, s), 2.83 (2H, q, J=7.4 Hz), 2.74 (3H, s), 1.32 (3H, t, J=7.6 Hz).

STEP 8. 3-[4-(2-Chloroethyl)phenyl]-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-

5 b]pyridine-6-carbonitrile

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-ethyl-3-[4-(2-hydroxyethyl)phenyl]-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridine-6-carbonitrile (step 7).

TLC Rf = 0.8 (hexane/ethyl acetate = 1:1).

10 STEP 9. 3-[4-(2-Azidoethyl)phenyl]-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-
b]pyridine-6-carbonitrile

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[4-(2-chloroethyl)phenyl]-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridine-6-carbonitrile (step 8).

15 ¹H-NMR (CDCl₃) δ 7.46 (2H, d, J=8.1 Hz), 7.33 (2H, d, J=8.2 Hz), 3.62 (2H, t, J=7.1 Hz), 3.02 (2H, t, J=7.1 Hz), 2.86 (3H, s), 2.82 (2H, q, J=7.6 Hz), 2.73 (3H, s), 1.31 (3H, t, J=7.6 Hz).

STEP 10. 3-[4-(2-Aminoethyl)phenyl]-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-
b]pyridine-6-carbonitrile

20 The title compound was prepared according to the procedure described in step 9 of Example 1 from 3-[4-(2-azidoethyl)phenyl]-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridine-6-carbonitrile (step 9).

TLC Rf = 0.05 (hexane/ethyl acetate = 1:1).

STEP 11. 6-Cyano-2-ethyl-5,7-dimethyl-3-(4-{2-[(4-
25 methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3H-imidazo[4,5-
b]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 3-[4-(2-aminoethyl)phenyl]-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-6-carbonitrile (step 10).

mp 133 °C; MS (ESI) m/z 517.12 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.78 (2H, d, J=8.1 Hz), 7.37-7.25 (6H, m), 6.46 (1H, br.s), 3.56-3.54 (2H, m), 2.92 (2H, t, J=7.0 Hz), 2.85 (3H, s), 2.76 (2H, q, J=6.0 Hz), 2.68 (3H, s), 2.41 (3H, s), 1.29 (3H, t, J=6.2 Hz).

EXAMPLE 42

2-ETHYL-4,6-DIMETHYL-1-(4-{2-[(4-

METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PH
ENYL)-1H-IMIDAZO[4,5-c]PYRIDINE

STEP 1. 2-{4-[(2,6-Dimethyl-3-nitro-4-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 4-chloro-2,6-dimethyl-3-nitropyridine (Tanaka, A.; et al. *J.Med.Chem.*, 1999, 41, 4408.) and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 8.74 (1H, br.s), 7.31 (2H, d, J=8.2 Hz), 7.18 (2H, d, J=8.2 Hz), 6.68 (1H, s), 3.95-3.89 (2H, m), 2.91 (2H, t, J=6.6 Hz), 2.72 (3H, s), 2.36 (3H, s).

STEP 2. 2-{4-[(3-Amino-2,6-dimethyl-4-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 4 of Example 1 from 2-{4-[(2,6-dimethyl-3-nitro-4-pyridinyl)amino]phenyl}ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.19 (2H, d, J=8.4 Hz), 7.01 (2H, d, J=8.6 Hz), 6.76 (1H, s), 5.82 (1H, br.s), 3.87 (2H, t, J=6.4 Hz), 3.18 (2H, br.s), 2.85 (2H, t, J=6.4 Hz), 2.44 (3H, s), 2.35 (3H, s).

STEP 3. 2-[4-(2-Ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl
propionate

A mixture of 2-{4-[(3-amino-2,6-dimethyl-4-pyridinyl)amino]phenyl} ethanol (step 2, 2.4 g, 9.3 mmol), propionic anhydride (13 mL, 101 mmol) and propionic acid (13 mL, 174 mmol) was stirred at 120 °C for 16h. After cooling, the mixture was diluted with 2N aqueous NaOH (150 mL) and extracted with

dichloromethane (3 x 150 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with dichloromethane/methanol (gradient elution from 20:1 to 10:1) afforded 2.3 g (69 %) of the title compound as a brown oil: ¹H-NMR (CDCl₃) δ 7.44 (2H, d, J=8.1 Hz), 7.27 (2H, d, J=8.2 Hz), 6.72 (1H, s), 4.38 (2H, t, J=6.9 Hz), 3.07 (2H, t, J=7.1 Hz), 2.88 (3H, s), 2.82 (2H, q, J=7.6 Hz), 2.56 (3H, s), 2.36 (2H, q, J=7.6 Hz), 1.29 (3H, t, J=7.6 Hz), 1.15 (3H, t, J=7.7 Hz).

STEP 4. 2-[4-(2-Ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.46 (2H, d, J=8.1 Hz), 7.26 (2H, d, J=8.1 Hz), 6.73 (1H, s), 4.00 (2H, t, J=6.6 Hz), 3.01 (2H, t, J=6.4 Hz), 2.88 (3H, s), 2.81 (2H, q, J=7.5 Hz), 2.54 (3H, s), 1.29 (3H, t, J=7.5 Hz).

STEP 5. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethanol (step 4).

TLC Rf = 0.1 (ethyl acetate).

STEP 6. 1-[4-(2-Azidoethyl)phenyl]-2-ethyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridine

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-4,6-dimethyl-1*H*-

imidazo[4,5-*c*]pyridine (step 5).

¹H-NMR (CDCl₃) δ 7.46 (2H, d, J=8.0 Hz), 7.29 (2H, d, J=7.7 Hz), 6.72 (1H, s), 3.62 (2H, t, J=6.9 Hz), 3.02 (2H, t, J=6.9 Hz), 2.88 (3H, s), 2.81 (2H, q, J=7.4 Hz), 2.56 (3H, s), 1.29 (3H, t, J=7.6 Hz).

STEP 7. 2-[4-(2-Ethyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 1-[4-(2-azidoethyl)phenyl]-2-ethyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridine (step 6).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.2 Hz), 7.26 (2H, d, J=8.4 Hz), 6.73 (1H, s), 3.08 (2H, t, J=6.9 Hz), 2.90-2.78 (4H, m), 2.88 (3H, s), 2.56 (3H, s), 1.30 (3H, t, J=7.3 Hz).

STEP 8. 2-Ethyl-4,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-imidazo[4,5-*c*]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethylamine (step 7).

mp 143 °C; MS (ESI) m/z 492.12 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.77 (2H, d, J=8.3 Hz), 7.38 (2H, d, J=8.4 Hz), 7.25 (2H, d, J=8.4 Hz), 7.20 (2H, d, J=8.4 Hz), 6.77 (1H, s), 3.58-3.51 (2H, m), 2.92 (2H, t, J=7.0 Hz), 2.89 (3H, s), 2.79 (2H, q, J=7.5 Hz), 2.53 (3H, s), 2.38 (3H, s), 1.28 (3H, t, J=7.5 Hz).

EXAMPLE 43

2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2-[4-(2-Nitroanilino)phenyl]ethanol

- 5 The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-chloronitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.47 (1H, s), 8.21 (1H, dd, J=1.5, 8.8 Hz), 7.40-7.16 (6H, m), 6.81-6.70 (1H, m), 3.91 (2H, t, J=6.5 Hz), 2.90 (2H, t, J=6.5 Hz).

STEP 2. 2-[4-(2-Aminoanilino)phenyl]ethanol

- 10 The title compound was prepared according to the procedure described in step 4 of Example 1 from 2-[4-(2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.15-6.96 (4H, m), 6.82-6.66 (4H, m), 5.14 (1H, s), 3.80 (2H, t, J=6.6 Hz), 3.75 (2H, br.s), 2.79 (2H, t, J=6.6 Hz).

STEP 3. 2-[4-(2-Ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

- 15 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-aminoanilino)phenyl]ethanol (step 2) and propionyl chloride.

MS (EI) m/z 322 (M⁺); ¹H-NMR (CDCl₃) δ 7.79 (1H, d, J=7.7 Hz), 7.43 (2H, d, J=8.6 Hz), 7.34-7.06 (5H, m), 4.38 (2H, t, J=7.0 Hz), 3.07 (2H, t, J=7.0 Hz), 2.80 (2H, q, J=7.5 Hz), 2.36 (2H, q, J=7.6 Hz), 1.35 (3H, t, J=7.5 Hz), 1.15 (3H, t, J=7.6 Hz).

STEP 4. 2-[4-(2-Ethyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

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¹H-NMR (CDCl₃) δ 7.81-7.75 (1H, m), 7.45 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=8.3 Hz), 7.25-7.08 (3H, m), 3.98 (2H, t, J=6.5 Hz), 3.00 (2H, t, J=6.5 Hz), 2.80 (2H, q, J=7.5 Hz), 1.26 (3H, t, J=7.5 Hz).

STEP 5. 2-[4-(2-Ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

- 5 The title compound was prepared according to the procedure described in step 5 Example 26 from 2-[4-(2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4). MS (EI) m/z 291 (M⁺); ¹H-NMR (CDCl₃) δ 7.81-7.76 (1H, m), 7.43 (2H, d, J=8.3 Hz), 7.40-7.06 (5H, m), 3.62 (2H, t, J=6.5 Hz), 3.04 (2H, t, J=6.5 Hz), 2.80 (2H, q, J=7.5 Hz), 1.27 (3H, t, J=7.5 Hz).

10 STEP 6. 2-[4-(2-Ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

- 15 ¹H-NMR (CDCl₃) δ 7.80-7.74 (1H, m), 7.45-7.06 (7H, m), 3.06 (2H, t, J=6.5 Hz), 2.89 (2H, t, J=6.5 Hz), 2.76 (2H, q, J=7.5 Hz), 1.26 (3H, t, J=7.5 Hz).

STEP 7. 2-Ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole

- The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 7.75 (1H, d, J=8.8 Hz), 7.71 (2H, d, J=8.3 Hz), 7.39- 7.14 (8H, m), 7.07 (1H, d, J=8.8 Hz), 6.68 (1H, br.s), 3.62-3.54 (2H, m), 2.94 (2H, t, J=6.3 Hz), 2.79 (2H, q, J=7.0 Hz), 2.41 (3H, s), 1.33 (3H, t, J=7.0 Hz).

EXAMPLE 44

- 25 2-[4-(2-ETHYL-1H-BENZIMIDAZOL-1-YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4 of Example 43).

¹H-NMR (CDCl₃) δ 7.93 (2H, d, J=8.3 Hz), 7.85-7.75 (2H, m), 7.40- 7.15 (7H, m), 7.08 (1H, d, J=8.8 Hz), 4.77 (1H, br.s) 4.36 (2H, t, J=6.4 Hz),, 3.00 (2H, t, J=6.4 Hz), 2.78 (2H, q, J=7.0 Hz), 2.44 (3H, s), 1.32 (3H, t, J=7.0 Hz).

EXAMPLE 45

4-METHYL-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2-[4-(3-Methyl-2-nitroanilino)phenyl]ethanol

A mixture of 2-nitro-3-methylaniline (Newman, M.S.; Kannan R. *J. Org. Chem.*, 1976, 41, 3356., 1.9 g, 12.4 mmol), 4-bromophenylethyl alcohol (2.5 g, 12.4 mmol), K₂CO₃ (1.7 g, 12.4 mmol) and CuI (230 mg, 1.24 mmol) was placed in a sealed tube and heated at 200 °C for 2 h. After cooling, the mixture was poured into water (100 mL) and extracted with ethyl acetate (300 mL). The organic layer was washed with 2N aqueous NaOH (100 mL) and brine (100 mL), then dried (Na₂SO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to afford 700 mg (21%) of the title compound as an orange oil: ¹H-NMR (CDCl₃) δ 7.77 (1H, br.s), 7.09-7.45 (6H, m), 6.69 (1H, d, J=6.3 Hz), 3.83 (2H, t, J=6.6 Hz), 2.82 (2H, t, J=6.6 Hz), 2.59 (3H, s).

STEP 2. 2-[4-(2-Amino-3-methylanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 26 from 2-[4-(3-methyl-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.02 (2H, d, J=8.2 Hz), 6.95 (1H, d, J=7.7 Hz), 6.91 (1H, d, J=7.0 Hz), 6.65 (1H, dd, J=7.0 Hz, 7.7 Hz), 6.62 (2H, d, J=8.2 Hz), 5.15 (1H, br.s), 3.75 (2H, t, J=6.6 Hz), 2.73 (2H, t, J=6.6 Hz), 2.19 (3H, s).

STEP 3. 2-[4-(2-Ethyl-4-methyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-3-methylanilino)phenyl]ethanol (step 2) and propionyl chloride.

TLC Rf = 0.6 (hexane: ethyl acetate = 1:1).

STEP 4. 2-[4-(2-Ethyl-4-methyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-4-methyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.41-7.43 (2H, m), 7.29 (2H, d, J=6.4 Hz), 7.07 (2H, d, J=6.4 Hz), 6.91-6.94 (1H, m), 3.97 (2H, t, J=6.6 Hz), 2.99 (2H, t, J=6.6 Hz), 2.84 (2H, q, J=7.5 Hz), 2.71 (3H, s), 1.27 (3H, t, J=7.5 Hz).

STEP 5. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-4-methyl-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-4-methyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 7.43 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 7.07-7.09 (2H, m), 6.90-6.95 (1H, m), 3.81 (2H, t, J=7.2 Hz), 3.19 (2H, t, J=7.2 Hz), 2.84 (2H, q, J=7.5 Hz), 2.72 (3H, s), 1.27 (3H, t, J=7.5 Hz).

STEP 6. 2-[4-(2-Ethyl-4-methyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-4-methyl-1H-benzimidazole (step 5).

¹H-NMR (CDCl₃) δ 7.43 (2H, d, J=8.0 Hz), 7.31 (2H, d, J=8.0 Hz), 7.05-7.09 (2H, m), 6.90-6.94 (1H, m), 3.61 (2H, t, J=7.0 Hz), 3.01 (2H, t, J=7.0 Hz), 2.84 (2H, q, J=7.5 Hz), 2.72 (3H, s), 1.27 (3H, t, J=7.5 Hz).

STEP 7. 2-[4-(2-Ethyl-4-methyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine

- 5 The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-4-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 6).

¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.3 Hz), 7.28 (2H, d, 8.3 Hz), 7.04-7.11 (2H, m), 6.86-6.95 (1H, m), 3.07 (2H, t, J=6.6 Hz), 2.87 (2H, t, J=6.6 Hz), 2.84 (2H, q, J=7.5 Hz), 2.71 (3H, s), 1.27 (3H, t, J=7.5 Hz).

STEP 8. 2-Ethyl-4-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

- 15 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-4-methyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 7).

MS (ESI) *m/z* 477 (M + H)⁺; ¹H-NMR (DMSO-*d*₆) δ 7.65 (2H, d, J=7.7 Hz), 7.33-7.41 (4H, m), 7.15 (2H, d, J=7.7 Hz), 7.01-7.07 (2H, m), 6.86 (1H, d, J=6.8 Hz), 3.19 (2H, br.s), 2.68-2.74 (4H, m), 2.56 (3H, s), 2.28 (3H, s), 1.21 (3H, t, J=7.1 Hz); IR (KBr) *v*_{max} 3390, 1602, 1519, 1429, 1230, 1130, 1085 cm⁻¹.

EXAMPLE 46

4-METHYL-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

- 25 The title compound was prepared according to the procedure described in Example 2 from 2-ethyl-4-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)

amino}ethyl}phenyl)-1*H*-benzimidazole (Example 45).

¹H-NMR (DMSO-*d*₆) δ 7.65 (2H, d, *J*=7.7 Hz), 7.33-7.41 (4H, m), 7.15 (2H, d, *J*=7.7 Hz), 7.01-7.07 (2H, m), 6.86 (1H, d, *J*=6.8 Hz), 3.19 (2H, br.s), 2.68-2.74 (4H, m), 2.56 (3H, s), 2.28 (3H, s), 1.21 (3H, t, *J*=7.1 Hz); IR (KBr) ν_{max} 3390, 1602, 1519, 1429, 1230, 1130, 1085 cm⁻¹.

EXAMPLE 47

2-ETHYL-5-METHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL)PHENYL)-1*H*-BENZIMIDAZOLE

10 STEP 1. 2-[(4-Methyl-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 1 of Example 45 from 4-methyl-2-nitroaniline and 4-iodophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.35 (1H, br.s), 8.00 (1H, s), 7.33-7.09 (6H, m), 3.91-3.89 (2H, m), 2.89 (2H, t, *J*=6.4 Hz), 2.30 (3H, s).

15 STEP 2. 2-[(2-Amino-4-methylanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[(4-methyl-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.05 (2H, d, *J*=8.3 Hz), 6.98 (1H, d, *J*=7.7 Hz), 6.67-6.64 (3H, m), 6.58-6.55 (1H, m), 5.06 (1H, br.s), 3.80-3.78 (4H, m), 2.77 (2H, t, *J*=6.4 Hz), 2.28 (3H, s).

20 STEP 3. 2-[4-(2-Ethyl-5-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-4-methylanilino)phenyl]ethanol (step 2) and propionyl chloride.

25 TLC R_f = 0.33 (hexane/ethyl acetate = 2:1).

STEP 4. 2-[4-(2-Ethyl-5-methyl-1*H*-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-Ethyl-5-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.55 (1H, s), 7.43 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 6.99-6.95 (2H, m), 3.99 (2H, t, J=6.6 Hz), 3.00 (2H, t, J=6.6 Hz), 2.77 (2H, q, J=7.7 Hz), 2.47 (3H, s), 1.32 (3H, t, J=7.7 Hz)

STEP 5. 2-[4-(2-Ethyl-5-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(2-ethyl-5-methyl-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 4).

TLC Rf = 0.74 (Hexane/ethyl acetate = 1:1).

STEP 6. 2-[4-(2-Ethyl-5-methyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-5-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 7.55 (1H, s), 7.43 (2H, d, J=8.2 Hz), 7.29 (2H, d, J=8.2 Hz), 7.01-6.95 (2H, m), 4.85 (2H, br.s), 3.30-3.25 (2H, m), 3.16-3.11 (2H, m), 2.76 (2H, q, J=7.6 Hz), 2.45 (3H, s), 1.31 (3H, t, J=7.6 Hz).

STEP 7. 2-Ethyl-5-methyl-1-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-5-methyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (DMSO-*d*₆) δ 7.76 (2H, d, J=8.4 Hz), 7.42-7.36 (6H, m), 7.00-6.91 (2H, m), 6.53-6.49 (1H, m), 3.29-3.24 (2H, m), 2.79-2.65 (4H, m), 2.40 (3H, s), 2.33 (3H, s), 1.20 (3H, t, J=7.4 Hz).

EXAMPLE 48

2-ETHYL-5-METHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in

- 5 Example 2 from 2-ethyl-5-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole (Example 47).

¹H-NMR (DMSO-d₆) δ 7.60 (2H, d, J=7.7 Hz), 7.42-7.33 (5H, m), 7.13 (2H, d, J=7.7 Hz), 6.96 (2H, m), 3.16 (2H, m), 2.71-2.66 (4H, m), 2.39 (3H, s), 2.27 (3H, s), 1.20 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 1599, 1514, 1285, 1232, 1130, 1086 cm⁻¹.

EXAMPLE 49

2-BUTYL-5-METHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}BUTYL}PHENYL)-1H-BENZIMIDAZOLE

- 15 STEP 1. 2-[4-(2-Butyl-5-methyl-1H-benzimidazol-1-yl)phenyl]ethyl pentanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-4-methylanilino)phenyl]ethanol (step 2 of Example 47) and pentanoyl chloride.

- 20 ¹H-NMR (CDCl₃) δ 7.56-7.55 (1H, m), 7.43-7.40 (2H, m), 7.29-7.26 (2H, m), 7.02-6.94 (2H, m), 4.38 (2H, t, J=6.9 Hz), 3.06 (2H, t, J=6.9 Hz), 2.75 (2H, t, J=7.4 Hz), 2.47 (3H, s), 2.33 (2H, t, J=7.4 Hz), 1.80-1.55 (4H, m), 1.41-1.23 (4H, m), 0.94-0.83 (6H, m).

STEP 2. 2-[4-(2-Butyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethanol

- 25 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-butyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethyl pentanoate (step 1).

¹H-NMR (CDCl₃) δ 7.55 (1H, s), 7.44 (2H, d, J=8.2 Hz), 7.27 (2H, d, J=8.2 Hz), 7.02-6.95 (2H, m), 3.99 (2H, t, J=6.6 Hz), 3.01 (2H, t, J=6.6 Hz), 2.75 (2H, t, J=7.3 Hz), 2.47 (3H, s), 1.79-1.68 (2H, m), 1.36-1.23 (2H, m), 0.85 (3H, t, J=7.3 Hz).

5 STEP 3. 2-[4-(2-Butyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(2-butyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 2).

¹H-NMR (CDCl₃) δ 7.56 (1H, s), 7.42 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.03-6.95 (2H, m), 3.61 (2H, t, J=6.9 Hz), 3.01 (2H, t, J=6.9 Hz), 2.75 (2H, t, J=7.3 Hz), 2.47 (3H, s), 1.80-1.68 (2H, m), 1.37-1.26 (2H, m), 0.85 (3H, t, J=7.3 Hz).

10 STEP 3. 2-[4-(2-Butyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-butyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 2).

¹H-NMR (CDCl₃) δ 7.55 (1H, s), 7.40 (2H, d, J=8.3 Hz), 7.26 (2H, d, J=8.3 Hz), 7.01-6.94 (2H, m), 3.15 (2H, t, J=7.3 Hz), 2.98 (2H, t, J=7.3 Hz), 2.74 (2H, t, J=7.7 Hz), 2.46 (3H, s), 1.77-1.67 (2H, m), 1.35-1.28 (2H, m), 0.84 (3H, t, J=7.7 Hz).

20 STEP 4. 2-Butyl-5-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-butyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 3).

¹H-NMR (CDCl₃) δ 7.76 (2H, d, J=8.2 Hz), 7.54 (1H, m), 7.31-7.21 (6H, m), 7.03-6.95 (2H, m), 6.67-6.63 (1H, m), 3.61-3.54 (2H, m), 2.91 (2H, t, J=7.1 Hz), 2.73 (2H, t, J=7.3 Hz), 2.47 (3H, s), 2.40 (3H, s), 1.76-1.65 (2H, m), 1.36-1.28 (2H, m), 0.83 (3H, t, J=7.3 Hz).

5 EXAMPLE 50

2-BUTYL-5-METHYL-1-(4-{2-[[{(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL]AMINO}BUTYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in

- 10 Example 2 from 2-butyl-5-methyl-1-(4-{2-[[{(4-methylphenyl)sulfonyl]amino}carbonyl]amino]ethyl}phenyl)-1H-benzimidazole (Example 49).

mp 130-140 °C; ¹H-NMR (DMSO-d₆) δ 7.59 (2H, d, J=7.8 Hz), 7.40-7.31 (5H, m), 7.11 (2H, d, J=7.8 Hz), 6.98-6.92 (2H, m), 3.15 (2H, m), 2.71-2.66 (4H, m), 2.39 (3H, s), 2.26 (3H, s), 1.67-1.57 (2H, m), 1.31-1.21 (2H, m), 0.79 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 1599, 1514, 1400, 1130, 1086 cm⁻¹.

15 EXAMPLE 51

6-METHYL-2-ETHYL-3-(4-{2-[[{(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL]AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

20 STEP 1. 2-[4-(5-Methyl-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-fluoro-4-methylnitrobenzene and 4-aminophenylethyl alcohol.

- 25 ¹H-NMR (CDCl₃) δ 9.51 (1H, br.s), 8.10 (1H, d, J=8.8 Hz), 7.20-7.31 (4H, m), 6.98 (1H, s), 6.58 (1H, d, J=8.4 Hz), 3.91 (2H, t, J=6.4 Hz), 2.89 (t, J=6.4 Hz), 2.27 (3H, s).

STEP 2. 2-[4-(2-Amino-5-methylanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 26 from 2-[4-(5-methyl-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.07 (2H, d, J=8.3 Hz), 6.93 (1H, s), 6.81 (1H, d, J=8.1 Hz), 6.70-6.72 (3H, m), 3.81 (2H, t, J=6.4 Hz), 3.61 (2H, br.s), 2.78 (2H, t, J=6.4 Hz), 2.22 (3H, s).

STEP 3. 2-[4-(2-Ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-Amino-5-methylanilino)phenyl]ethanol (step 2) and propionyl chloride.

¹H-NMR (CDCl₃) δ 7.64 (1H, d, J=8.3 Hz), 7.42 (2H, d, J=8.0 Hz), 7.28 (2H, d, J=8.0 Hz), 7.08 (1H, d, J=8.3 Hz), 6.87 (1H, s), 4.38 (2H, t, J=6.9 Hz), 3.06 (2H, t, J=6.9 Hz), 2.76 (2H, q, J=7.5 Hz), 2.41 (3H, s), 2.36 (2H, q, J=7.7 Hz), 1.35 (3H, t, J=7.5 Hz), 1.15 (3H, t, J=7.7 Hz).

STEP 4. 2-[4-(2-Ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in 6 of Example 1 from 2-[4-(2-ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.64 (1H, d, J=8.1 Hz), 7.45 (2H, d, J=8.1 Hz), 7.19-7.30 (2H, m), 7.08 (1H, d, J=8.1 Hz), 6.88 (1H, s), 3.99 (2H, t, J=6.6 Hz), 3.00 (2H, t, J=6.6 Hz), 2.77 (2H, q, J=7.6 Hz), 2.40 (3H, s), 1.33 (3H, t, J=7.6 Hz).

STEP 5. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-6-methyl-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 7.65 (1H, d, J=8.2 Hz), 7.43 (2H, d, J=8.2 Hz), 7.31 (2H, d, J=8.2 Hz), 7.07 (1H, d, J=8.2 Hz), 6.88 (1H, s), 3.82 (2H, t, J=7.0 Hz), 3.19 (2H, t, 7.0 Hz), 2.77 (2H, q, J=7.6 Hz), 2.41 (3H, s), 1.33 (3H, t, J=7.6 Hz).

STEP 6. 2-[4-(2-Ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

- 5 The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-6-methyl-1H-benzimidazole (step 5).

¹H-NMR (CDCl₃) δ 7.64 (1H, d, J=8.2 Hz), 7.43 (2H, d, J=8.2 Hz), 7.31 (2H, d, J=8.2 Hz), 7.08 (1H, d, J=8.2 Hz), 6.87 (1H, s), 3.62 (2H, t, J=7.0 Hz), 3.01 (2H, t, J=7.0 Hz), 2.77 (2H, q, J=7.6 Hz), 2.37 (3H, s), 1.33 (3H, t, J=7.6 Hz).

STEP 7. 2-[4-(2-Ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethyl azide (step 6).

- 15 ¹H-NMR (CDCl₃) δ 7.64 (1H, d, J=8.3 Hz), 7.40 (2H, d, J=8.2 Hz), 7.28 (2H, d, J=8.2 Hz), 7.07 (1H, d, J=8.3 Hz), 6.88 (1H, s), 3.07 (2H, br.s), 2.87 (2H, t, J=6.8 Hz), 2.76 (2H, q, J=7.6 Hz), 2.40 (3H, s), 1.33 (3H, t, J=7.6 Hz).

STEP 8. 6-Methyl-2-Ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole

- 20 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethylamine (step 7).

¹H-NMR (CDCl₃) δ 7.73 (2H, d, J=8.3 Hz), 7.66 (1H, d, J=8.0 Hz), 7.27-7.38 (6H, m), 7.09 (1H, d, J=8.0 Hz), 6.88 (1H, s), 3.59-3.63 (2H, m), 2.95 (2H, t, J=6.6 Hz), 2.77 (2H, q, J=7.5 Hz), 2.41 (3H, s), 2.39 (3H, s), 1.33 (3H, t, J=7.5 Hz).

EXAMPLE 52

6-METHYL-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

- 5 The title compound was prepared according to the procedure described in Example 2 from 6-methyl-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole (Example 51).

mp 151-165 °C; ¹H-NMR (DMSO-d₆) δ 7.64 (2H, d, J=8.0 Hz), 7.51 (1H, d, J=8.2 Hz), 7.33-7.42 (4H, m), 7.15 (2H, d, J=8.0 Hz), 7.02 (1H, dd, J=1.4 Hz, 8.2 Hz), 6.87 (1H, s), 3.18 (2H, br.s), 2.65-2.78 (4H, m), 2.34 (3H, s), 2.78 (3H, s), 1.21 (3H, t, J=7.6 Hz).

- 10

EXAMPLE 53

7-METHYL-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE

- 15

STEP 1. 2-[4-(2-Methyl-6-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 1 Example 45 from 6-methyl-2-nitroaniline and 4-bromophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 8.28 (1H, br.s), 7.96 (1H, d, J=8.4 Hz), 7.39-7.44 (1H, m), 7.02-7.12 (3H, m), 6.72 (2H, d, J=8.4 Hz), 3.82 (2H, t, J=6.5 Hz), 2.81 (2H, t, J=6.5 Hz), 2.08 (3H, s).

- 20

STEP 2. 2-[4-(2-Amino-6-methylanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 26 from 2-[4-(2-methyl-6-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 6.97-7.03 (3H, m), 6.66 (2H, d, J=7.6 Hz), 6.52 (2H, d, J=7.6 Hz), 4.97 (1H, br.s), 3.86 (2H, br.s), 3.79 (2H, t, J=6.4 Hz), 2.76 (2H, t, J=6.4 Hz), 2.16 (3H, s).

- 25

STEP 3. 2-[4-(2-Ethyl-7-methyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-6-methylanilino)phenyl]ethanol (step 2) and propionyl chloride.

- 5 TLC Rf = 0.6 (hexane:ethyl acetate = 1:1).

STEP 4. 2-[4-(2-Ethyl-7-methyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-7-methyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

- 10 ¹H-NMR (CDCl₃) δ 7.63 (1H, d, J=8.0 Hz), 7.38-7.41 (2H, m), 7.26-7.31 (2H, m), 7.14 (1H, dd, J=7.4 Hz, 8.0 Hz), 6.91 (1H, d, J=7.4 Hz), 3.98 (2H, t, J=6.6 Hz), 3.01 (2H, t, J=6.6 Hz), 2.63 (2H, q, J=7.5 Hz), 1.89 (3H, s), 1.31 (3H, t, J=7.5 Hz).

STEP 5. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-7-methyl-1H-benzimidazole

- 15 The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-7-methyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

- ¹H-NMR (CDCl₃) δ 7.64 (1H, d, J=8.1 Hz), 7.26-7.39 (4H, m), 7.14 (1H, dd, J=7.4 Hz, 8.1 Hz), 6.91 (1H, d, J=7.4 Hz), 3.81 (2H, t, J=7.2 Hz), 3.19 (2H, d, J=7.2 Hz), 2.63 (2H, q, J=7.6 Hz), 1.88 (3H, s), 1.32 (3H, t, J=7.6 Hz).

STEP 6. 2-[4-(2-Ethyl-7-methyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-7-methyl-1H-benzimidazole (step 5).

- 25 ¹H-NMR (CDCl₃) δ 7.64 (1H, d, J=7.4 Hz), 7.39 (2H, d, J=8.0 Hz), 7.31 (2H, d, J=8.0 Hz), 7.14 (1H, dd, J=7.4 Hz, 8.1 Hz), 6.91 (1H, d, J=8.1 Hz), 3.61 (2H, t,

J=6.8 Hz), 3.02 (2H, t, J=6.8 Hz), 2.63 (2H, q, J=7.6 Hz), 1.89 (3H, s), 1.31 (3H, t, J=7.5 Hz).

STEP 7. 2-[4-(2-Ethyl-7-methyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-7-methyl-1H-benzimidazol-1-yl)phenyl]ethyl azide (step 6).

¹H-NMR (CDCl₃) δ 7.64 (1H, d, J=7.9 Hz), 7.36 (2H, d, J=8.2 Hz), 7.28 (2H, d, J=8.2 Hz), 7.14 (1H, dd, J=7.5 Hz, 7.9 Hz), 6.91 (1H, d, J=7.5 Hz), 3.06 (2H, t, J=6.8 Hz), 2.87 (2H, t, J=6.8 Hz), 2.63 (2H, q, J=7.5 Hz), 1.89 (3H, s), 1.32 (3H, t, J=7.5 Hz).

STEP 8. 2-Ethyl-7-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-7-methyl-1H-benzimidazol-1-yl)phenyl]ethylamine (step 7).

MS (ESI) m/z 477 (M + H)⁺, ¹H-NMR (CDCl₃) δ 7.75 (2H, d, J=8.3 Hz), 7.62 (1H, d, J=7.9 Hz), 7.28-7.33 (5H, m), 7.14 (2H, d, J=7.6 Hz), 6.91 (1H, d, J=7.9 Hz), 6.72 (1H, br.s), 3.58 (2H, d, J=6.8 Hz), 2.93 (2H, t, J=6.8 Hz), 2.62 (2H, q, J=7.6 Hz), 2.41 (3H, s), 1.86 (3H, s), 1.29 (3H, t, J=7.6 Hz).

EXAMPLE 54

7-METHYL-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 2-ethyl-7-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)

amino]ethyl}phenyl)-1*H*-benzimidazole (Example 53).

¹H-NMR (DMSO-d₆) δ 7.63 (2H, d, J=7.4 Hz), 7.47 (1H, d, J=8.1 Hz), 7.36 (4H, s), 7.15 (2H, d, J=7.7 Hz), 7.06 (1H, dd, J=7.2 Hz, 8.1 Hz), 6.87 (1H, d, J=7.2 Hz), 5.99 (1H, br.s), 3.16 (2H, br.s), 2.76 (2H, br.s), 2.52 (2H, q, J=7.6 Hz), 2.28 (3H, s), 1.82 (3H, s), 1.19 (3H, t, J=7.6 Hz); IR (KBr) ν_{max} 3400, 1610, 1525, 1290, 1132, 1095, 820, 751 cm⁻¹.

EXAMPLE 55

4-CHLORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-[4-(3-Chloro-2-nitroanilino)phenyl]ethanol

A mixture of 2,6-dichloronitrobenzene (Norman, M.H.; Chen, N.; et al. *PCT Int. Appl.*, WO 9940091 (1999)., Spada, A.P.; Fink, C.A.; Myers, M.R. *PCT Int. Appl.*, WO 9205177 (1992)., 6.3 g, 32.8 mmol), 4-aminophenylethyl alcohol (4.9 g, 36 mmol) and sodium acetate (3.2 g, 39.3 mmol) was placed in a sealed tube and heated at 160 °C for 3 h. After cooling, the mixture was poured into water (100 mL) and extracted with ethyl acetate (300 mL). The organic layer was washed with 2N aqueous NaOH (100 mL) and brine (100 mL), then dried (Na₂SO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to afford 4.57 g (72%) of the title compound as a red oil: ¹H-NMR (CDCl₃) δ 7.09-7.28 (6H, m), 6.91 (1H, dd, J=2.0, 7.1 Hz), 3.87 (2H, t, J=6.6 Hz), 2.86 (2H, t, J=6.6 Hz).

STEP 2. 2-[4-(2-Amino-3-chloroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[4-(3-chloro-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.06-7.10 (3H, m), 7.00 (1H, dd, J=1.0 Hz, 7.9 Hz), 6.62-6.73 (3H, m), 5.16 (1H, br.s), 4.14 (2H, br.s), 3.81 (2H, t, J=6.1 Hz), 2.77 (2H, t, J=6.1 Hz).

STEP 3. 2-[4-(4-Chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-3-chloroanilino)phenyl]ethanol (step 2) and propionyl chloride.

TLC Rf = 0.5 (hexane: ethyl acetate = 1:1).

STEP 4. 2-[4-(4-Chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(4-Chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.45 (2H, d, J=8.6 Hz), 7.26-7.31 (3H, m), 7.09 (1H, d, J=7.9 Hz), 6.96 (1H, dd, J=0.9 Hz, 7.9 Hz), 3.99 (2H, t, J=6.6 Hz), 3.00 (2H, t, J=6.6 Hz), 2.84 (2H, q, J=7.5 Hz), 1.30 (3H, t, J=7.5 Hz).

STEP 5. 4-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(4-chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 7.45 (2H, d, J=8.6 Hz), 7.30 (2H, d, J=8.6 Hz), 7.27 (1H, s), 7.10 (1H, d, J=8.1 Hz), 6.98 (1H, d, J=8.1 Hz), 3.81 (2H, t, J=7.1 Hz), 3.19 (2H, t, J=7.1 Hz), 2.84 (2H, q, J=7.6 Hz), 1.31 (3H, t, J=7.6 Hz).

STEP 6. 2-[4-(4-Chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 4-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole (step 5).

¹H-NMR (CDCl₃) δ 7.45 (2H, d, J=8.2 Hz), 7.29-7.33 (3H, m), 7.10 (1H, dd, J=8.1 Hz, 7.7 Hz), 6.96 (1H, d, J=7.7 Hz), 3.62 (2H, t, J=7.1 Hz), 3.02 (2H, t, J=7.1 Hz), 2.84 (2H, q, J=7.6 Hz), 1.30 (3H, t, J=7.6 Hz).

STEP 7. 2-[4-(4-Chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

- 5 The title compound was prepared according to the procedure described in step 7 of Example 37 from 2-[4-(4-chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide (step 6).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.1 Hz), 7.29-7.33 (3H, m), 7.09 (1H, dd, J=7.7 Hz, 7.9 Hz), 7.99 (1H, d, J=7.9 Hz), 3.07 (2H, t, J=6.8 Hz), 2.87 (2H, t, J=6.8 Hz), 2.85 (2H, q, J=7.6 Hz), 1.30 (3H, t, J=7.6 Hz).

STEP 8. 4-Chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino[ethyl]phenyl)-1H-benzimidazole

- 15 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(4-chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine (step 7).

MS (ESI) m/z 498 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.73 (2H, d, J=8.5 Hz), 7.28-7.38 (7H, m), 7.09 (1H, d, J=7.9 Hz), 6.97 (1H, d, J=7.9 Hz), 6.69 (1H, br.s), 3.58 (2H, t, J=6.9 Hz), 2.94 (2H, t, J=6.9 Hz), 2.83 (2H, q, J=7.5 Hz), 2.40 (3H, s), 1.31 (3H, t, J=7.5 Hz).

EXAMPLE 56

4-CHLORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO[ETHYL]PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

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The title compound was prepared according to the procedure described in Example 2 from 4-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole (Example 54).

- 5 ¹H-NMR (DMSO-d₆) δ 7.62 (2H, d, J=8.0 Hz), 7.41 (4H, s), 7.29 (1H, d, J=6.6 Hz), 7.12-7.18 (3H, m), 7.02-7.04 (1H, m), 3.18 (2H, br.s), 2.70-2.79 (4H, m), 2.27 (3H, s), 1.23 (3H, t, J=7.4 Hz); IR (KBr) ν_{max} 3385, 1602, 1519, 1433, 1174, 1130, 1085, 813 cm⁻¹.

EXAMPLE 57

- 10 5-CHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-[4-(4-Chloro-2-nitroanilino)phenyl]ethanol

- 15 The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,5-dichloronitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.42 (1H, s), 8.20 (1H, d, J=2.0Hz), 7.35-7.10 (6H, m), 3.96-3.85 (2H, m), 2.91 (2H, t, J=7.0 Hz).

STEP 2. 2-[4-(2-Amino-4-chloroanilino)phenyl]ethanol

- 20 The title compound was prepared according to the procedure described in step 3 of Example 6 from 2-[4-(4-chloro-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.30-7.05 (4H, m), 6.83-6.62 (3H, m), 5.15 (1H, br.s), 3.86-3.75 (2H, m), 3.75 (2H, br.s), 2.77 (2H, t, J=7.0 Hz).

STEP 3. 2-[4-(5-Chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate

- 25 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-4-chloroanilino)phenyl]ethanol (step 2) and propionyl chloride.

¹H-NMR (CDCl₃) δ 7.75 (1H, d, J=2.0 Hz), 7.43 (2H, d, J=8.0 Hz), 7.28 (2H, d, J=8.0 Hz), 7.15 (1H, dd, J=2.0, 8.6 Hz), 6.99 (1H, d, J=8.6 Hz), 4.38 (2H, t, J=7.0 Hz), 3.07 (2H, t, J=7.0 Hz), 2.78 (2H, q, J=7.5 Hz), 2.36 (2H, q, J=7.5 Hz), 1.24 (3H, t, J=7.5 Hz), 1.15 (3H, t, J=7.5 Hz).

5 STEP 4. 2-[4-(5-Chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5-chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

10 ¹H-NMR (CDCl₃) δ 7.75 (1H, d, J=2.0 Hz), 7.46 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.15 (1H, dd, J=2.0, 8.6 Hz), 7.00 (1H, d, J=8.6 Hz), 3.99 (2H, t, J=6.5 Hz), 3.00 (2H, t, J=6.5 Hz), 2.78 (2H, q, J=7.5 Hz), 1.26 (3H, t, J=7.5 Hz).

STEP 5. 2-[4-(5-Chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 Example 26 from 2-[4-(5-chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 4).

15 MS (EI) m/z 325 (M⁺); ¹H-NMR (CDCl₃) δ 7.75 (1H, d, J=2.0 Hz), 7.45 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 7.15 (1H, dd, J=2.0, 8.6 Hz), 6.99 (1H, d, J=8.6 Hz), 3.62 (2H, t, J=7.0 Hz), 3.02 (2H, t, J=7.0 Hz), 2.78 (2H, q, J=7.5 Hz), 1.26 (3H, t, J=7.5 Hz).

20 STEP 6. 2-[4-(5-Chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 2-[4-(5-chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

25 ¹H-NMR (CDCl₃) δ 7.75 (1H, d, J=2.0 Hz), 7.41 (2H, d, J=8.3 Hz), 7.27 (2H, d, J=8.3 Hz), 7.14 (1H, dd, J=2.0, 8.6 Hz), 6.99 (1H, d, J=8.6 Hz), 3.08 (2H, t, J=7.0 Hz), 2.86 (2H, t, J=7.0 Hz), 2.77 (2H, q, J=7.5 Hz), 1.34 (3H, t, J=7.5 Hz).

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STEP 7. 5-Chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(5-chloro-2-ethyl-1H-benzimidazol-1-

yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 7.76 (1H, d, J=1.8 Hz), 7.72 (2H, d, J=8.4 Hz), 7.39 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.3 Hz), 7.17 (1H, dd, J=8.6, 1.8 Hz), 7.00 (1H, d, J=8.6 Hz), 6.73 (1H, br.s), 3.59-3.53 (2H, m), 2.94 (2H, t, J=7.0 Hz), 2.81 (2H, q, J=7.5 Hz), 1.34 (3H, t, J=7.5 Hz).

EXAMPLE 58

2-[4-(5-CHLORO-2-ETHYL-1H-BENZIMIDAZOL-1-YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(5-chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4 of Example 57).

¹H-NMR (CDCl₃) δ 7.92 (2H, d, J=8.4 Hz), 7.74 (1H, d, J=2.0 Hz), 7.34 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz), 7.23 (2H, d, J=8.4 Hz), 7.16 (1H, dd, J=8.5, 2.0 Hz), 6.99 (1H, d, J=8.5 Hz), 4.74 (1H, br.s), 4.37 (2H, t, J=6.8 Hz), 3.01 (2H, t, J=6.8 Hz), 2.75 (2H, q, J=7.6 Hz), 1.33 (3H, t, J=7.6 Hz).

EXAMPLE 59

6-CHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2-[(5-Chloro-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4-dichloronitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.52 (1H, br.s), 8.16 (1H, d, J=9.2Hz), 7.33 (2H, d, J=8.2 Hz), 7.25 (2H, d, J=8.2 Hz), 7.13 (1H, d, J=2.2 Hz), 6.71 (1H, dd, J=9.2, 2.2 Hz), 3.92 (q, 2H, J=6.4 Hz), 2.92 (t, 2H, J=6.4 Hz).

STEP 2. 2-[(2-Amino-5-chloroanilino)phenyl]ethanol

- 5 The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[(5-chloro-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.12-7.09 (3H, m), 6.92 (1H, dd, J=8.4, 2.4 Hz), 6.78-6.70 (3H, m), 5.16 (1H, br.s), 3.83 (2H, t, J=6.6 Hz), 2.81 (2H, t, J=6.6 Hz).

STEP 3. 2-[4-(6-Chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate

- 10 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-5-chloroanilino)phenyl]ethanol (step 2) and propionyl chloride.

¹H-NMR (CDCl₃) δ 7.67 (1H, d, J=8.6 Hz), 7.44 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 7.22 (1H, dd, J=8.4, 2.0 Hz), 7.07 (1H, d, J=2.0 Hz), 4.38 (2H, t, J=7.0 Hz), 3.07 (2H, t, J=7.0 Hz), 2.77 (2H, q, J=7.5 Hz), 2.36 (2H, q, J=7.5 Hz), 1.35 (3H, t, J=7.5 Hz), 1.15 (3H, t, J=7.5 Hz).

STEP 4. 2-[4-(6-Chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethanol

- 20 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.67 (1H, d, J=8.6 Hz), 7.46 (2H, d, J=8.6 Hz), 7.30-7.26 (3H, m), 7.22 (1H, dd, J=8.6, 2.2 Hz), 7.08 (1H, d, J=2.0 Hz), 3.99 (2H, q, J=6.4 Hz), 3.01 (2H, t, J=6.4 Hz), 2.78 (2H, q, J=7.6 Hz), 1.72 (1H, t, J=5.6 Hz), 1.35 (3H, t, J=7.6 Hz).

- 25 STEP 5. 2-[4-(6-Chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(6-chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 4).

MS (EI) *m/z* 325 (*M*⁺).

5 STEP 6. 2[4-(6-Chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(6-chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 7.67 (1H, d, *J*=8.6 Hz), 7.41 (2H, d, *J*=8.4 Hz), 7.31-7.19 (3H, m), 7.12 (1H, d, *J*=2.0 Hz), 4.66 (2H, br.s), 3.23-3.17 (2H, m), 3.08-3.04 (2H, m), 2.75 (2H, q, *J*=7.5 Hz), 1.33 (3H, t, *J*=7.5 Hz).

STEP 7. 6-Chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(6-chloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 7.74 (2H, d, *J*=8.4 Hz), 7.67 (1H, d, *J*=8.4 Hz), 7.37 (2H, d, *J*=8.4 Hz), 7.30-7.20 (6H, m), 7.05 (1H, d, *J*=2.0 Hz), 6.73 (1H, m), 3.62-3.55 (2H, m), 2.93 (2H, t, *J*=7.2 Hz), 2.77 (2H, t, *J*=7.5 Hz), 1.32 (3H, t, *J*=7.5 Hz).

20 EXAMPLE 60

6-CHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in

Example 2 from 6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole (Example 59).

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¹H-NMR (DMSO-d₆) δ 7.64 (1H, d, J=8.6 Hz), 7.59 (2H, d, J=8.1 Hz), 7.38 (4H, m), 7.22 (1H, dd, J=8.6, 2.0 Hz), 7.11 (2H, d, J=8.1 Hz), 7.05 (1H, d, J=2.0 Hz), 3.15 (2H, m), 2.74 - 2.66 (4H, m), 2.25 (3H, s), 1.21 (3H, t, J=7.4 Hz); IR (KBr) ν_{max} 1601, 1516, 1398, 1178, 1130, 1084 cm⁻¹.

5 **EXAMPLE 61**

4-(6-CHLORO-2-ETHYL-1H-BENZIMIDAZOL-1-YL)PHENETHYL-(4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(6-chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4 of Example 59).

mp 183-187 °C; ¹H-NMR (DMSO-d₆) δ 7.75 (2H, d, J=8.1 Hz), 7.66 (1H, d, J=8.6 Hz), 7.43 (4H, s), 7.40 (2H, d, J=8.1 Hz), 7.24 (1H, dd, J=8.6, 2.0 Hz), 7.03 (1H, d, J=2.0 Hz), 4.27 (2H, t, J=6.6 Hz), 2.95 (2H, t, J=6.6 Hz), 2.70 (2H, q, J=7.5 Hz), 2.34 (3H, s), 1.22 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 1744, 1516, 1352, 1225, 1165 cm⁻¹.

EXAMPLE 62

2-BUTYL-6-CHLORO-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]BUTYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2-[4-(2-Butyl-6-chloro-1H-benzimidazol-1-yl)phenyl]ethyl pentanoate
The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-5-chloroanilino)phenyl]ethanol (step 2 of Example 59) and pentanoyl chloride.

¹H-NMR (CDCl₃) δ 7.66 (1H, d, J=8.4 Hz), 7.44 (2H, d, J=8.1 Hz), 7.28 (2H, d, J=8.1 Hz), 7.22 (1H, dd, J=8.4, 2.0 Hz), 7.06 (1H, d, J=2.0 Hz), 4.38 (2H, t, J=6.8 Hz), 3.07 (2H, t, J=6.8 Hz), 2.74 (2H, t, J=7.7 Hz), 2.33 (2H, t, J=7.5 Hz), 1.81-1.70 (2H, m), 1.66-1.56 (2H, m), 1.40-1.28 (4H, m), 0.94-0.84 (6H, m).

STEP 2. 2-[4-(2-Butyl-6-chloro-1*H*-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-butyl-6-chloro-1*H*-benzimidazol-1-yl)phenyl]ethyl pentanoate (step 1).

- 5 ¹H-NMR (CDCl₃) δ 7.66 (1H, d, J=8.6 Hz), 7.46 (2H, d, J=8.1 Hz), 7.29-7.26 (2H, m), 7.22 (1H, dd, J=8.6, 2.0 Hz), 7.07 (1H, d, J=2.0 Hz), 4.00 (2H, q, J=6.4 Hz), 3.01 (2H, t, J=6.4 Hz), 2.75 (2H, t, J=7.5 Hz), 2.24-2.19 (1H, m), 1.81-1.71 (2H, m), 1.37-1.26 (2H, m), 0.87 (3H, t, J=7.3 Hz)

STEP 3. 2-[4-(2-Butyl-6-chloro-1*H*-benzimidazol-1-yl)phenyl]ethyl azide

- 10 The title compound was prepared according to the procedure described in step 4 of Example 1 from 2-[4-(2-butyl-6-chloro-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 2).

- ¹H-NMR (CDCl₃) δ 7.66 (1H, d, J=8.6 Hz), 7.45 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 7.22 (1H, dd, J=8.6, 2.0 Hz), 7.07 (1H, d, J=2.0 Hz), 3.62 (2H, t, J=7.0 Hz), 3.02 (2H, t, J=7.0 Hz), 2.74 (2H, t, J=7.5 Hz), 1.80-1.70 (2H, m), 1.40-1.26 (2H, m), 0.86 (2H, t, J=7.3 Hz)

STEP 3. 2-[4-(2-Butyl-6-chloro-1*H*-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-butyl-6-chloro-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 2).

- 20 ¹H-NMR (CDCl₃) δ 7.66 (1H, d, J=8.6 Hz), 7.43 (2H, d, J=8.2 Hz), 7.27 (2H, d, J=8.2 Hz), 7.21 (1H, dd, J=8.6, 2.0 Hz), 7.08 (1H, d, J=2.0 Hz), 3.11 (2H, t, J=7.1 Hz), 2.91 (2H, t, J=7.1 Hz), 2.74 (2H, t, J=7.4 Hz), 1.81-1.70 (2H, m), 1.41-1.27 (2H, m), 0.86 (3H, t, J=7.4 Hz)

- 25 STEP 4. 2-Butyl-6-chloro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-butyl-6-chloro-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 3).

¹H-NMR (CDCl₃) δ 7.75 (2H, d, J=8.4 Hz), 7.66 (1H, d, J=8.2 Hz), 7.38 (2H, d, J=8.4 Hz), 7.30-7.20 (6H, m), 7.05 (1H, d, J=2.0 Hz), 6.77-6.72 (1H, m), 3.61-3.55 (2H, m), 2.96-2.92 (2H, m), 2.74 (2H, t, J=7.5 Hz), 2.39 (3H, s), 1.78-1.67 (2H, m), 1.35-1.26 (2H, m), 0.84 (3H, t, J=7.3 Hz).

EXAMPLE 63

2-BUTYL-6-CHLORO-1-(4-{2-[(4-METHYLPHENYL)SULFONYLAMINO]CARBONYLAMINO}BUTYL}PHENYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 2-butyl-6-chloro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole (Example 62).

mp 137-145 °C; ¹H-NMR (DMSO-d₆) δ 7.65-7.63 (1H, m), 7.59 (2H, d, J=7.8 Hz), 7.38 (4H, s), 7.23-7.20 (1H, m), 7.12 (2H, d, J=7.8 Hz), 7.04 (1H, s), 3.15 (2H, m), 2.72-2.67 (4H, m), 2.26 (3H, s), 1.66-1.61 (2H, m), 1.29-1.22 (2H, m), 0.79 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 1603, 1520, 1458, 1396, 1130, 1086 cm⁻¹.

EXAMPLE 64

7-CHLORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYLAMINO]CARBONYLAMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-[4-(2-Chloro-6-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,3-dichloronitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 8.11 (1H, br.s), 8.00 (1H, dd, J=1.5 Hz, 8.5 Hz), 7.61 (1H, dd, J=1.5 Hz, 7.9 Hz), 7.12 (2H, d, J=8.4 Hz), 7.03 (1H, dd, J=7.9 Hz, 8.5 Hz), 6.80 (2H, d, J=8.4 Hz), 3.82 (2H, t, J=6.6 Hz), 2.81 (2H, d, J=6.6 Hz).

STEP 2. 2-[4-(2-Amino-6-chloroanilino)phenyl]ethanol

- 5 The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[4-(2-chloro-6-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.04 (2H, d, J=7.8 Hz), 6.97 (1H, dd, J=7.9 Hz, 8.0 Hz), 6.82 (1H, dd, J=1.5 Hz, 7.9 Hz), 6.66 (1H, dd, J=1.5 Hz, 8.0 Hz), 6.59 (2H, d, J=7.8 Hz), 5.36 (1H, br.s), 3.94 (2H, br.s), 3.78 (2H, t, J=6.6 Hz), 2.75 (2H, d, J=6.6 Hz).

- 10

STEP 3. 2-[4-(7-Chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-6-chloroanilino)phenyl]ethanol (step 2) and propionyl chloride.

- 15 TLC R_f = 0.6 (hexane : ethyl acetate = 1:1).

STEP 4. 2-[4-(7-Chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-amino-6-chloroanilino)phenyl]ethyl propionate (step 3).

- 20 ¹H-NMR (CDCl₃) δ 7.68 (1H, dd, J=1.9 Hz, 7.0 Hz), 7.39 (2H, d, J=8.2 Hz), 7.28 (2H, d, J=8.2 Hz), 7.11-7.20 (2H, m), 3.97 (2H, t, J=6.6 Hz), 3.01 (2H, t, J=6.6 Hz), 2.65 (2H, q, J=7.6 Hz), 1.32 (3H, t, J=7.6 Hz).

STEP 5. 7-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole

- 25 The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(7-chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 7.69 (1H, dd, J=2.2 Hz, 7.1 Hz), 7.37 (2H, d, J=8.2 Hz), 7.31 (2H, d, J=8.2 Hz), 7.11-7.17 (2H, m), 3.81 (2H, t, J=7.3 Hz), 3.19 (2H, t, J=7.3 Hz), 2.65 (2H, q, J=7.5 Hz), 1.33 (3H, t, J=7.5 Hz).

STEP 6. 2-[4-(7-Chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

- 5 The title compound was prepared according to the procedure described in step 8 of Example 1 from 7-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole (step 5).

¹H-NMR (CDCl₃) δ 7.69 (1H, dd, J=1.8 Hz, 7.4 Hz), 7.38 (2H, d, J=8.2 Hz), 7.34 (2H, d, J=8.2 Hz), 7.11-7.28 (2H, m), 3.60 (2H, t, J=7.0 Hz), 3.02 (2H, t, J=7.0 Hz), 2.64 (2H, q, J=7.6 Hz), 1.32 (3H, t, J=7.6 Hz).

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STEP 7. 2-[4-(7-Chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 2-[4-(7-chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide (step 6).

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¹H-NMR (CDCl₃) δ 7.69 (1H, d, J=7.9 Hz), 7.35 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 7.11-7.19 (2H, m), 3.06 (2H, t, J=6.8 Hz), 2.88 (2H, t, J=6.8 Hz), 2.65 (2H, q, J=7.5 Hz), 1.33 (3H, t, J=7.5 Hz).

STEP 8. 7-Chloro-2-ethyl-1-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino[ethyl]phenyl)-1H-benzimidazole

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The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(7-chloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine (step 7).

MS (ESI) m/z 498 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.74 (2H, d, J=8.4 Hz), 7.69 (1H, dd, J=1.9 Hz, 7.4 Hz), 7.29-7.32 (6H, m), 7.11-7.20 (2H, m), 6.72 (1H, br.s), 3.59 (2H, t, J=6.9 Hz), 2.93 (2H, t, J=6.9 Hz), 2.64 (2H, q, J=7.6 Hz), 2.42 (3H, s), 1.31 (3H, t, J=7.6 Hz).

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EXAMPLE 65

7-CHLORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

- 5 The title compound was prepared according to the procedure described in Example 2 from 7-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole (Example 64).

¹H-NMR (DMSO-d₆) δ 7.62-7.64 (3H, m), 7.31-7.39 (4H, m), 7.14-7.20 (4H, m), 6.00 (1H, br.s), 3.17 (2H, br.s), 2.75 (2H, br.s), 2.55 (2H, q, J=7.8 Hz), 2.29 (3H, s), 1.21 (3H, t, J=7.8 Hz); IR (KBr) ν_{max} 3380, 2891, 1605, 1520, 1425, 1285, 1126, 1075, 798 cm⁻¹.

EXAMPLE 66

- 15 5-FLUORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2-[4-(4-Fluoro-2-nitroanilino)phenyl]ethanol

- The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,5-difluoronitrobenzene and 4-aminophenylethyl alcohol.
- 20 ¹H-NMR (CDCl₃) δ 9.32 (1H, s), 7.88-7.93 (1H, m), 7.11-7.30 (5H, m), 3.90 (2H, t, J=6.2 Hz), 2.90 (2H, t, J=6.2 Hz).

STEP 2. 2-[4-(2-Amino-4-fluoroanilino)phenyl]ethanol

- The title compound was prepared according to the procedure described in step 2 of Example 26 from 2-[4-(4-fluoro-2-nitroanilino)phenyl]ethanol (step 1).
- 25 ¹H-NMR (CDCl₃) δ 6.98-7.06 (3H, m), 6.60 (2H, d, J=8.2 Hz), 6.49 (1H, dd, J=2.8 Hz, 12.8 Hz), 6.41 (1H, dd, J=2.8 Hz, 8.4 Hz), 4.99 (1H, br.s), 3.94 (2H, br.s), 3.79 (2H, br.s), 2.76 (2H, t, J=6.4 Hz).

STEP 3. 2-[4-(2-Ethyl-5-fluoro-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-4-fluoroanilino)phenyl]ethanol (step 2) and propionyl chloride.

- 5 MS (EI) m/z 340 (M^+).

STEP 4. 2-[4-(2-Ethyl-5-fluoro-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-amino-4-fluoroanilino)phenyl]ethyl propionate (step 3).

- 10 $^1\text{H-NMR}$ (CDCl_3) δ 7.40-7.47 (3H, m), 7.28 (2H, d, $J=8.0$ Hz), 6.88-7.02 (2H, m), 3.98 (2H, t, $J=6.3$ Hz), 3.01 (2H, t, $J=6.3$ Hz), 2.78 (2H, q, $J=7.5$ Hz), 1.34 (3H, t, $J=7.5$ Hz).

STEP 5. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-5-fluoro-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-5-fluoro-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

- 15 $^1\text{H-NMR}$ (CDCl_3) δ 7.42-7.46 (3H, m), 7.31 (2H, d, $J=8.1$ Hz), 6.89-7.02 (2H, m), 3.81 (2H, t, $J=7.1$ Hz), 3.19 (2H, t, $J=7.1$ Hz), 2.78 (2H, q, $J=7.6$ Hz), 1.35 (3H, t, $J=7.6$ Hz).

- 20 STEP 6. 2-[4-(2-Ethyl-5-fluoro-1H-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-5-fluoro-1H-benzimidazole (step 5).

- 25 $^1\text{H-NMR}$ (CDCl_3) δ 7.43-7.45 (3H, m), 7.31 (2H, d, $J=8.2$ Hz), 6.89-7.02 (2H, m), 3.62 (2H, t, $J=7.0$ Hz), 3.01 (2H, t, $J=7.0$ Hz), 2.77 (2H, q, $J=7.5$ Hz), 1.34 (3H, t, $J=7.5$ Hz).

STEP 7. 2-[4-(2-Ethyl-5-fluoro-1H-benzimidazol-1-yl)phenyl]ethylamine

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The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-5-fluoro-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 6).

¹H-NMR (CDCl₃) δ 7.40-7.46 (3H, m), 7.27-7.29 (2H, m), 6.87-6.99 (2H, m), 3.06 (2H, t, J=7.1 Hz), 2.87 (2H, t, J=7.1 Hz), 2.78 (2H, q, J=7.5 Hz), 1.35 (3H, t, J=7.5 Hz).

STEP 8. 5-Fluoro-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-5-fluoro-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 7).

MS (ESI) m/z 481 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.73 (2H, d, J=8.2 Hz), 7.35-7.45 (3H, m), 7.24-7.29 (4H, m), 6.87-7.00 (2H, m), 6.73 (1H, br.s), 3.57 (2H, t, J=7.0 Hz), 2.93 (2H, t, J=7.0 Hz), 2.77 (2H, q, J=7.6 Hz), 2.39 (3H, s), 1.31 (3H, t, J=7.6 Hz).

EXAMPLE 67

5-FLUORO-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBOXYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 5-fluoro-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole (Example 66).

mp 135-146 °C; MS (ESI) m/z 481 (M + H)⁺; ¹H-NMR (DMSO-d₆) δ 7.62 (2H, d, J=8.1 Hz), 7.39-7.48 (5H, m), 6.97-7.15 (4H, m), 5.92 (1H, br.s), 2.67-2.76 (4H, m), 2.51 (2H, br.s), 2.27 (3H, s), 1.23 (3H, t, J=7.6Hz).

EXAMPLE 68

2-BUTYL-6-FLUORO-1-{2-[4-(4-METHYLPHENYL)SULFONYLAMINO}CARBONYLAMINO]ETHYL}-1H-BENZIMIDAZOLE
STEP 1. 2-[4-(5-Fluoro-2-nitroanilino)phenyl]ethanol

- 5 The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4-difluoronitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.61 (1H, br.s), 8.26 (1H, dd, J=6.1, 9.5 Hz), 7.32 (2H, d, J=8.2 Hz), 7.22 (2H, d, J=8.3 Hz), 6.78 (1H, dd, J=2.6, 11.3 Hz), 6.47 (1H, ddd, J=2.2, 7.2, 9.7 Hz), 3.91 (2H, dt, J=6.2, 6.2 Hz), 2.91 (2H, t, J=6.4 Hz), 1.52 (1H, t, J=5.7 Hz).

STEP 2. 2-[4-(2-Amino-5-fluoroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[4-(5-fluoro-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.12 (2H, d, J=8.4 Hz), 6.87 (1H, dd, J=2.7, 10.1 Hz), 6.83 (2H, d, J=8.4 Hz), 6.72 (1H, dd, J=5.7, 8.6 Hz), 6.63 (1H, ddd, J=2.7, 8.4, 8.4 Hz), 5.30 (1H, s), 3.83 (2H, t, J=6.4 Hz), 2.80 (2H, t, J=6.4 Hz).

STEP 3. 2-[4-(2-butyl-6-fluoro-1H-benzimidazol-1-yl)phenyl]ethyl pentanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-5-fluoroanilino)phenyl]ethanol (step 2) and pentanoyl chloride.

¹H-NMR (CDCl₃) δ 7.67 (1H, dd, J=4.8, 8.8 Hz), 7.44 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.1 Hz), 7.04-6.95 (1H, m), 6.76 (1H, dd, J=2.6, 8.8 Hz), 4.38 (2H, t, J=6.8 Hz), 3.07 (2H, t, J=6.8 Hz), 2.74 (2H, t, J=7.5 Hz), 2.33 (2H, t, J=7.7 Hz), 1.81-1.55 (4H, m), 1.42-1.25 (4H, m), 6.91 (3H, t, J=7.3 Hz), 0.87 (3H, t, J=7.3 Hz).

STEP 4. 2-[4-(2-butyl-6-fluoro-1H-benzimidazol-1-yl)phenyl]ethanol

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The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-butyl-6-fluoro-1*H*-benzimidazol-1-yl)phenyl]ethyl pentanoate (step 3).

¹H-NMR (CDCl₃) δ 7.67 (1H, dd, J=4.8, 8.8 Hz), 7.46 (2H, d, J=8.2 Hz), 7.28 (2H, d, J=8.3 Hz), 6.99 (1H, ddd, J=2.4, 9.0, 9.5 Hz), 4.10-3.85 (2H, m), 3.01 (2H, t, J=6.4 Hz), 2.74 (2H, t, J=7.7 Hz), 1.84-1.69 (2H, m), 1.41-1.27 (2H, m), 0.87 (3H, t, J=7.3 Hz).

STEP 5. 2-[4-(2-Butyl-6-fluoro-1*H*-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(2-butyl-6-fluoro-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 4).

MS (EI) m/z 337 (M⁺); ¹H-NMR (CDCl₃) δ 7.68 (1H, dd, J=4.8, 8.8 Hz), 7.45 (2H, d, J=8.1 Hz), 7.30 (2H, d, J=8.1 Hz), 7.04-6.94 (1H, m), 6.77 (1H, dd, J=2.4, 8.6 Hz), 3.62 (2H, t, J=7.0 Hz), 3.02 (2H, t, J=6.8 Hz), 2.74 (2H, t, J=7.7 Hz), 1.86-1.69 (2H, m), 1.41-1.2 (2H, m), 0.86 (3H, t, J=7.3 Hz).

STEP 6. 2-[4-(2-Butyl-6-fluoro-1*H*-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 2-[4-(2-butyl-6-fluoro-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 7.67 (1H, dd, J=4.8, 8.8 Hz), 7.42 (2H, d, J=8.1 Hz), 7.27 (2H, d, J=8.2 Hz), 7.05-6.95 (1H, m), 6.78 (1H, dd, J=2.6, 8.6 Hz), 3.08 (2H, t, J=7.1 Hz), 2.88 (2H, t, J=6.8 Hz), 2.75 (2H, t, J=7.5 Hz), 1.82-1.69 (2H, m), 1.41-1.24 (2H, m), 0.87 (3H, t, J=7.3 Hz).

STEP 7. 2-Butyl-6-fluoro-3-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino]ethyl]phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-butyl-6-fluoro-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 7.73 (2H, d, J=8.4 Hz), 7.68 (1H, dd, J=4.6, 8.8 Hz), 7.38 (2H, d, J=8.4 Hz), 7.32-7.24 (4H, m), 7.00 (1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.75 (1H, dd, J=2.4, 8.6 Hz), 3.64-3.54 (2H, m), 2.94 (2H, t, J=7.0 Hz), 2.74 (2H, d, J=7.5 Hz), 1.80-1.65 (2H, m), 1.40-1.20 (2H, m), 0.84 (3H, t, J=7.3 Hz).

EXAMPLE 69

2-BUTYL-6-FLUORO-1-(2-([(4-METHYLPHENYL)SULFONYL]AMINO}{CARBONYL}AMINO)ETHYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 2-butyl-6-fluoro-3-(4-{2-([(4-methylphenyl)sulfonyl]amino}{carbonyl}amino)ethyl}phenyl)benzimidazole (Example 69).

¹H-NMR (DMSO-d₆) δ 7.70-7.57 (3H, m), 7.39 (4H, br), 7.14 (2H, d, J=8.0 Hz), 7.11-7.02 (1H, m), 8.85 (1H, dd, J=2.4, 9.2 Hz), 3.48-3.34 (2H, m), 3.17 (2H, br), 2.80-2.65 (4H, m), 2.28 (3H, s), 1.72-1.55 (2H, m), 1.35-1.20 (2H, m), 0.80 (3H, t, J=7.1 Hz); IR (KBr) ν_{max} 3387, 2872, 1601, 1516, 1479, 1400, 1130, 1086 cm⁻¹.

EXAMPLE 70

2-ETHYL-6-FLUORO-1-(4-{2-([(4-METHYLPHENYL)SULFONYL]AMINO}{CARBONYL}AMINO)ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-[4-(6-Fluoro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-5-fluoroanilino)phenyl]ethanol (step 2 of Example 68) and propionyl chloride.

MS (EI) m/z 340 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 7.67 (1H, dd, $J=4.8, 8.8$ Hz), 7.43 (2H, d, $J=8.4$ Hz), 7.28 (2H, d, $J=8.4$ Hz), 6.99 (1H, ddd, $J=2.5, 8.8, 9.5$ Hz), 6.77 (1H, dd, $J=2.5, 8.8$ Hz), 4.38 (2H, t, $J=6.6$ Hz), 3.07 (2H, t, $J=6.6$ Hz), 2.79 (2H, q, $J=7.4$ Hz), 2.35 (2H, q, $J=7.4$ Hz), 1.35 (3H, t, $J=7.4$ Hz), 1.14 (3H, t, $J=7.4$ Hz).

STEP 2. 2-[4-(6-fluoro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-fluoro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 1).

$^1\text{H-NMR}$ (CDCl_3) δ 7.67 (1H, dd, $J=4.8, 8.8$ Hz), 7.45 (2H, d, $J=8.4$ Hz), 7.29 (2H, d, $J=8.4$ Hz), 6.99 (1H, ddd, $J=2.5, 8.8, 9.5$ Hz), 6.78 (1H, dd, $J=2.5, 8.8$ Hz), 3.99 (2H, t, $J=6.6$ Hz), 3.00 (2H, t, $J=6.6$ Hz), 2.77 (2H, q, $J=7.5$ Hz), 1.35 (3H, t, $J=7.5$ Hz).

STEP 3. 6-fluoro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 Example 1 from 2-[4-(6-fluoro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 2).

MS (EI) m/z 302 (M^+).

STEP 4. 2-[4-(6-Fluoro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 Example 1 from 6-fluoro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole (step 3).

MS (EI) m/z 309 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 7.68 (1H, dd, $J=4.8, 8.8$ Hz), 7.44 (2H, d, $J=8.3$ Hz), 7.31 (2H, d, $J=8.3$ Hz), 6.99 (1H, ddd, $J=2.5, 8.8, 9.6$ Hz), 6.77 (1H, dd, $J=2.5, 8.8$ Hz), 3.62 (2H, t, $J=6.9$ Hz), 3.02 (2H, t, $J=6.9$ Hz), 2.77 (2H, q, $J=7.4$ Hz), 1.34 (3H, t, $J=7.4$ Hz)

STEP 5. 2-[4-(6-Fluoro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 2-[4-(6-fluoro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 4).

¹H-NMR (CDCl₃) δ 7.68 (1H, dd, J=4.8, 8.8 Hz), 7.43 (2H, d, J=8.2 Hz), 7.28 (2H, d, J=8.2 Hz), 6.98 (1H, ddd, J=2.4, 8.8, 8.8 Hz), 6.82 (1H, dd, J=2.4, 8.8 Hz), 3.37 (2H, br.s), 3.18 (2H, t, J=7.1 Hz), 3.01 (2H, t, J=7.1 Hz), 2.76 (2H, q, J=7.5 Hz), 1.33 (3H, t, J=7.5 Hz).

STEP 6. 2-Ethyl-6-fluoro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(6-fluoro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 5).

¹H-NMR (CDCl₃) δ 7.73 (2H, d, J=8.4 Hz), 7.68 (1H, dd, J=8.7, 4.9 Hz), 7.37 (2H, d, J=8.4 Hz), 7.32-7.23 (4H, m), 7.00 (1H, ddd, J=9.5, 8.7, 2.5 Hz), 6.79-6.69 (2H, m), 3.63-3.53 (2H, m), 2.94 (2H, t, J=7.5 Hz), 2.76 (2H, q, J=7.5 Hz), 2.40 (3H, s), 1.32 (3H, t, J=7.5 Hz).

EXAMPLE 71

5-METHOXY-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-[4-(4-Methoxy-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-chloro-5-methoxynitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.33 (1H, br.s), 7.63 (1H, d, J=3.0 Hz), 7.17-7.27 (5H, m), 7.04-7.08 (1H, m), 3.88 (2H, br.s), 3.82 (3H, s), 2.88 (2H, t, J=6.6 Hz).

STEP 2. 2-[4-(2-Amino-4-methoxyanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 26 from 2-[4-(4-methoxy-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.03 (2H, d, J=8.6 Hz), 6.98 (1H, d, J=8.4 Hz), 6.59 (2H, d, J=8.6 Hz), 6.28-6.36 (2H, m), 3.77-3.85 (5H, m), 2.76 (2H, t, J=6.6 Hz).

5 STEP 3. 2-[4-(2-Ethyl-5-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-4-methoxyanilino)phenyl]ethanol (step 2).

10 ¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.0 Hz), 7.12-7.29 (3H, m), 6.97 (1H, d, J=8.8 Hz), 6.82 (1H, dd, J=2.4 Hz, 8.8 Hz), 4.37 (2H, t, J=6.7 Hz), 3.86 (3H, s), 3.05 (2H, t, J=6.7 Hz), 2.77 (2H, q, J=7.5 Hz), 2.36 (2H, q, J=7.5 Hz), 1.36 (3H, t, J=7.5 Hz), 1.14 (3H, t, J=7.5 Hz).

STEP 4 2-[4-(2-Ethyl-5-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethanol

15 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-5-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.43 (2H, d, J=8.2 Hz), 7.27-7.30 (3H, m), 6.98 (1H, d, J=8.8 Hz), 6.82 (1H, dd, J=2.3 Hz, 8.8 Hz), 3.98 (2H, t, J=6.5 Hz), 3.86 (3H, s), 2.99 (2H, t, J=6.5 Hz), 2.77 (2H, q, J=7.6 Hz), 1.33 (3H, t, J=7.6 Hz).

20 STEP 5. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-5-methoxy-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-5-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 4).

25 ¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.2 Hz), 7.26-7.33 (3H, m), 6.99 (1H, d, J=8.8 Hz), 6.82 (1H, dd, J=2.5 Hz, 8.8 Hz), 3.86 (3H, s), 3.81 (2H, t, J=7.2 Hz), 3.18 (2H, t, J=7.2 Hz), 2.78 (2H, q, J=7.6 Hz), 1.34 (3H, t, J=7.6 Hz).

09977761.101501

STEP 6. 1-[4-(2-Azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl methyl ether

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-5-methoxy-1*H*-benzimidazole (step 5).

- 5 ¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.4 Hz), 7.27-7.32 (3H, m), 6.98 (1H, d, J=8.8 Hz), 6.82 (1H, dd, J=2.3 Hz, 8.8 Hz), 3.87 (3H, s), 3.61 (2H, t, J=6.9 Hz), 3.01 (2H, t, J=6.9 Hz), 2.76 (2H, q, J=7.7 Hz), 1.34 (3H, t, J=7.7 Hz).

STEP 7. 2-[4-(2-Ethyl-5-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethylamine

- 10 The title compound was prepared according to the procedure described in step 9 of Example 1 from 1-[4-(2-azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl methyl ether (step 6).

¹H-NMR (CDCl₃) δ 7.39 (2H, d, J=8.2 Hz), 7.26-7.30 (3H, m), 6.99 (1H, d, J=8.7 Hz), 6.82 (1H, dd, J=2.3 Hz, 8.7 Hz), 3.86 (3H, s), 3.07 (2H, t, J=6.9 Hz), 2.84 (2H, t, J=6.9 Hz), 2.77 (2H, q, J=7.6 Hz), 1.34 (3H, t, J=7.6 Hz).

- 15 STEP 8. 5-Methoxy-2-Ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino[ethyl]phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-5-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 7).

- 20 ¹H-NMR (CDCl₃) δ 7.74 (2H, d, J=8.2 Hz), 7.23-7.34 (7H, m), 6.97 (1H, d, J=8.7 Hz), 6.82 (1H, dd, J=1.8 Hz, 8.7 Hz), 6.67 (1H, br.s), 3.86 (3H, s), 3.57 (2H, t, J=6.4 Hz), 2.92 (2H, t, 6.4 Hz), 2.75 (2H, q, J=7.6 Hz), 2.40 (3H, s), 1.31 (3H, t, J=7.6 Hz).

EXAMPLE 72

- 25 5-METHOXY-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO[ETHYL]PHENYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 5-methoxy-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole (Example 72).

- 5 mp 163-175 °C; ¹H-NMR (DMSO-*d*₆) δ 7.60 (2H, d, *J*=7.5 Hz), 7.34-7.41 (4H, m), 7.12-7.18 (3H, m), 6.97 (1H, d, *J*=8.7 Hz), 6.78 (1H, d, *J*=8.7 Hz), 3.78 (3H, s), 2.66-2.76 (4H, m), 2.50 (2H, br.s), 2.78 (3H, s), 1.22 (3H, t, *J*=7.6 Hz); IR (KBr) ν_{max} 3363, 2833, 1596, 1404, 1128, 1085, 1026, 950 cm⁻¹.

EXAMPLE 73

- 10 2-[4-(2-ETHYL-5-METHOXY-1*H*-BENZIMIDAZOLE-1-
YL)PHENYL]ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-ethyl-5-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 4 of Example 71)

- 15 mp 95-98 °C; MS (ESI) *m/z* 494 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.93 (2H, d, *J*=8.2 Hz), 7.23-7.30 (3H, m), 7.16 (2H, d, *J*=8.2 Hz), 7.06 (2H, d, *J*=8.3 Hz), 6.92 (1H, d, *J*=8.8 Hz), 6.81 (1H, dd, *J*=2.2 Hz, 8.6 Hz), 4.33 (2H, t, *J*=6.3 Hz), 3.84 (3H, s), 2.93 (2H, t, *J*=6.3 Hz), 2.68 (2H, q, *J*=7.5 Hz), 2.37 (3H, s), 1.22 (3H, t, *J*=7.5 Hz); IR (KBr) ν_{max} 1743, 1596, 1517, 1487, 1444, 1278, 1159,
20 1074, 813 cm⁻¹.

EXAMPLE 74

2-ETHYL-6-MRTHOXY-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL;PH
ENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-[(5-Methoxy-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-chloro-4-methoxynitrobenene and 4-aminophenylethyl alcohol.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ 9.74 (1H, br.s), 8.18 (1H, d, $J=9.5\text{ Hz}$), 7.30 (2H, d, $J=8.4\text{ Hz}$), 7.24 (2H, d, $J=8.4\text{ Hz}$), 6.55 (1H, d, $J=2.8\text{ Hz}$), 6.34 (1H, dd, $J=9.5, 2.8\text{ Hz}$), 3.90 (2H, m), 3.74 (3H, s), 2.90 (3H, t, $J=6.6\text{ Hz}$).

STEP 2. 2-[(2-Amino-5-methoxyanilino)phenyl]ethanol

- 10 The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[(5-methoxy-2-nitroanilino)phenyl]ethanol (step 1).

$^1\text{H-NMR}$ (CDCl_3) δ 7.09 (2H, d, $J=8.4\text{ Hz}$), 6.80 (2H, d, $J=8.4\text{ Hz}$), 6.76-6.73 (2H, m), 6.54 (1H, dd, $J=8.6, 2.8\text{ Hz}$), 3.81 (2H, t, $J=6.6\text{ Hz}$), 3.71 (3H, s), 2.79 (2H, t, $J=6.6\text{ Hz}$).

STEP 3. 2-[4-(2-Ethyl-6-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethyl

- 15 propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-5-methoxyanilino)phenyl]ethanol (step 2) and propionyl chloride.

MS (EI) m/z 352 (M^+).

- 20 STEP 4. 2-[4-(2-Ethyl-6-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-6-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

- 25 $^1\text{H-NMR}$ (CDCl_3) δ 7.63 (1H, d, $J=8.8\text{ Hz}$), 7.45 (2H, d, $J=8.3\text{ Hz}$), 7.29 (2H, d, $J=8.3\text{ Hz}$), 6.89 (1H, dd, $J=8.8, 2.6\text{ Hz}$), 6.56 (1H, d, $J=2.6\text{ Hz}$), 4.00 (2H, t, $J=6.6\text{ Hz}$), 3.75 (3H, s), 3.01 (2H, t, $J=6.6\text{ Hz}$), 2.74 (2H, q, $J=7.5\text{ Hz}$), 1.32 (3H, t, $J=7.5\text{ Hz}$).

STEP 5. 2-[4-(2-Ethyl-6-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 4 of Example 26 from 2-(4-(2-ethyl-6-methoxy-1*H*-benzimidazol-1-yl)phenyl)ethanol (step 4).

- 5 TLC R_f = 0.50 (hexane/ethyl acetate = 1:1).

STEP 6. 2-[4-(2-Ethyl-6-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-6-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

- 10 ¹H-NMR (CDCl₃) δ 7.65 (1H, d, J=8.8 Hz), 7.41 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 6.89 (1H, dd, J=8.8, 2.4 Hz), 6.56 (1H, d, J=2.4 Hz), 3.76 (3H, s), 3.09 (2H, t, J=7.0 Hz), 2.89 (2H, t, J=7.0 Hz), 2.75 (2H, q, J=7.5 Hz), 1.32 (3H, t, J=7.5 Hz).

STEP 7. 2-Ethyl-6-methoxy-1-(4-{2-[(4-(4-

- 15 methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-6-methoxy-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 6).

- 20 ¹H-NMR (CDCl₃) δ 7.75 (2H, d, J=8.2 Hz), 7.62 (1H, d, J=8.7 Hz), 7.35-7.23 (6H, m), 6.89 (1H, dd, J=8.7, 2.5 Hz), 6.66 (1H, m), 6.55 (1H, d, J=2.5 Hz), 3.72 (3H, s), 3.59-3.57 (2H, m), 2.93 (2H, t, J=7.0 Hz), 2.73 (2H, q, J=7.6 Hz), 1.29 (3H, t, J=7.6 Hz).

EXAMPLE 752-ETHYL-6-MRTHOXY-1-(4-{2-[(4-(4-

- 25 METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PH
ENYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 2-ethyl-6-methoxy-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole (Example 74).

- 5 ¹H-NMR (DMSO-d₆) δ 7.59 (2H, d, J=8.3 Hz), 7.50 (1H, d, J=8.8 Hz), 7.41-7.35 (4H, m), 7.12 (2H, d, J=8.3 Hz), 6.80 (1H, dd, J=8.8, 2.4 Hz), 6.53 (1H, d, J=2.4 Hz), 3.67 (3H, s), 3.15 (2H, m), 2.73-2.62 (4H, m), 1.19 (3H, t, J=7.7 Hz); IR (KBr) ν_{max} 1595, 1516, 1485, 1454, 1400, 1157, 1128, 1086 cm⁻¹.

EXAMPLE 76

- 10 5-TRIFLUOROMETHYL-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-[2-Nitro-4-(trifluoromethyl)anilino]phenyl}ethanol

- 15 The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-chloro-5-trifluoromethylnitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.68 (1H, br.s), 8.50 (1H, s), 7.51 (1H, dd, J=2.2 Hz, 9.2 Hz), 7.33 (2H, d, J=8.2 Hz), 7.19-7.26 (3H, m), 3.92 (2H, t, J=6.3 Hz), 2.92 (2H, t, J=6.3 Hz).

- 20 STEP 2. 2-[2-Amino-4-(trifluoromethyl)anilino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 2 of Example 26 from 2-[2-nitro-4-(trifluoromethyl)anilino]phenyl}ethanol (step 1).

- 25 ¹H-NMR (CDCl₃) δ 7.10-7.16 (3H, m), 6.97 (2H, d, J=8.2 Hz), 6.82 (2H, d, J=8.2 Hz), 3.82 (2H, t, J=6.6 Hz), 2.79 (2H, t, J=6.6 Hz).

STEP 3. 2-{4-[2-Ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[2-amino-4-(trifluoromethyl)anilino]phenyl} ethanol (step 2) and propionyl chloride.

¹H-NMR (CDCl₃) δ 8.05 (1H, s), 7.42-7.47 (2H, m), 7.27-7.31 (2H, m), 7.13 (2H, d, =8.4 Hz), 4.39 (2H, t, J=7.0 Hz), 3.08 (2H, t, J=7.0 Hz), 2.80 (2H, q, J=7.6 Hz), 2.36 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz), 1.14 (3H, t, J=7.6 Hz).

STEP 4. 2-{4-[2-Ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 8.05 (1H, s), 7.49 (1H, d, J=8.4 Hz), 7.44 (2H, d, J=8.6 Hz), 7.30 (2H, d, J=8.6 Hz), 7.16 (1H, d, J=8.4 Hz), 4.01 (2H, t, J=6.4 Hz), 3.03 (2H, t, J=6.4 Hz), 2.80 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

STEP 5. 2-{4-[2-Ethyl-5-(trifluoromethyl)-1H-benzimidazol-1yl]phenyl}ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-{4-[2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl} ethanol (step 4).

¹H-NMR (CDCl₃) δ: 8.05 (1H, s), 7.22-7.48 (5H, m), 7.15 (1H, d, J=8.4 Hz), 3.62 (2H, t, J=6.8 Hz), 3.02 (2H, t, J=6.8 Hz), 2.80 (2H, q, J=7.5 Hz), 1.36 (3H, t, J=7.5 Hz).

STEP 6. 2-{4-[2-Ethyl-5-(trifluoromethyl)-1H-benzimidazol-1yl]phenyl}ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-{4-[2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1yl]phenyl}ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 8.05 (1H, s), 7.44 (3H, d, J=8.8 Hz), 7.29 (2H, d, J=8.8 Hz), 7.16 (1H, d, J=8.6 Hz), 3.09 (2H, t, J=6.8 Hz), 2.89 (2H, t, J=6.8 Hz), 2.81 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

STEP 7. 5-Trifluoromethyl-2-ethyl-3-(4-{2-[(4-

methylphenyl)sulfonyl]amino}
carbonyl)amino]ethyl}phenyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-{4-[2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethylamine (step 6).

MS (ESI) m/z 533 (M + H)⁺; ¹H-NMR (CDCl₃) δ 8.03 (1H, s), 7.80 (2H, d, J=8.2 Hz), 7.73 (2H, d, J=8.2 Hz), 7.38-7.43 (3H, m), 7.26-7.29 (2H, m), 7.13 (1H, d, J=8.4 Hz), 6.70 (1H, br.s), 3.57 (2H, t, 6.7 Hz), 2.94 (2H, t, J=6.7 Hz), 2.80 (2H, q, J=7.6 Hz), 2.43 (3H, s), 1.34 (3H, t, J=7.6 Hz).

EXAMPLE 77

5-TRIFLUOROMETHYL-2-ETHYL-3-(4-{2-[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 5-trifluoromethyl-2-ethyl-3-(4-{2-[(4-

methylphenyl)sulfonyl]amino}
carbonyl)amino]ethyl}phenyl)-1H-benzimidazole (Example 76).

¹H-NMR (DMSO-d₆) δ 8.02 (1H, s), 7.61-7.66 (4H, m), 7.48-7.51 (1H, m), 7.24-7.28 (3H, m), 7.14 (2H, d, 7.9 Hz), 3.09 (2H, br.s), 2.60-2.83 (4H, m), 2.22 (3H, s), 1.13 (3H, t, J=7.5 Hz).

EXAMPLE 78

5-ACETYL-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 1-{4-[4-(2-Hydroxyethyl)anilino]-3-nitrophenyl}ethanone

- 5 A mixture of 2-chloro-5-acetylnitrobenzene (Oelschlaeger, H.; Schreiber, O. *Liebigs Ann. Chem.*, 1961, 641, 81., 2 g, 10 mmol) , 4-aminophenylethyl alcohol (1.64 g, 12 mmol) and NaHCO₃ (1 g, 12 mmol) in DMF (60 mL) was heated at 150 °C for 3 h. After cooling, the mixture was poured into water (100 mL) and extracted with ethyl acetate (300 mL). The organic layer was washed with 2N
- 10 aqueous NaOH (100 mL) and brine (100 mL), then dried (Na₂SO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to afford 1.36 g (45%) of the title compound as an orange oil; ¹H-NMR (CDCl₃) δ 9.83 (1H, br.s), 8.20 (1H, d, J=2.1 Hz), 7.94 (1H, dd, J=2.1 Hz, 9.3 Hz), 7.34 (2H, d, J=8.2 Hz), 7.24 (2H, d, J=8.2 Hz), 7.16
- 15 (1H, d, J=9.3 Hz), 3.91 (2H, t, J=6.6 Hz), 2.92 (2H, t, J=6.6 Hz), 2.57 (3H, s).

STEP 2. 1-{3-Amino-4-[4-(2-hydroxyethyl)anilino]phenyl}ethanone

The title compound was prepared according to the procedure described in step 4 of Example 1 from 1-{4-[4-(2-hydroxyethyl)anilino]-3-nitrophenyl}ethanone (step 1).

- 20 ¹H-NMR (CDCl₃) δ: 7.41 (1H, d, J=2.0 Hz), 7.37 (1H, dd, J=2.0 Hz, 8.2 Hz), 7.11-7.17 (3H, m), 6.94 (2H, d, J=8.2 Hz), 5.72 (1H, br.s), 3.85 (2H, t, J=6.6 Hz), 3.65 (2H, br.s), 2.83 (2H, t, J=6.6 Hz), 2.52 (3H, s).

STEP 3. 2-4-(5-Acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl)ethyl propionate

- 25 The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-{3-amino-4-[4-(2-hydroxyethyl)anilino]phenyl}ethanone (step 2) and propionyl chloride.
- TLC Rf = 0.4 (hexane/ethyl acetate = 1:1).

STEP 4. 1-{2-Ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazol-5-yl}ethyl propionate

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-4-(5-acetyl-2-ethyl-1*H*-benzimidazol-1-yl)phenyl)ethyl

5 propionate (step 3).

¹H-NMR (CDCl₃) δ 8.39 (1H, d, J=1.2 Hz), 7.89 (1H, dd, J=1.2 Hz, 8.6 Hz), 7.48 (2H, d, J=7.4 Hz), 7.30 (2H, d, J=7.4 Hz), 7.13 (1H, d, J=8.6 Hz), 4.00 (2H, t, J=6.4 Hz), 3.02 (2H, t, J=6.4 Hz), 2.80 (2H, q, J=7.6 Hz), 2.68 (3H, s), 1.38 (2H, t, J=7.6 Hz).

10 STEP 5. 1-{1-[4-(2-Chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}ethanone

The title compound was prepared according to the procedure described in step 7 of Example 1 from 1-{2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazol-5-yl}ethanone (step 4).

15 ¹H-NMR (CDCl₃) δ 8.40 (1H, d, J=1.2 Hz), 7.90 (1H, dd, J=1.2 Hz, 8.4 Hz), 7.47 (2H, d, J=8.4 Hz), 7.32 (2H, d, J=8.4 Hz), 7.13 (1H, d, J=8.4 Hz), 3.83 (2H, t, J=7.3 Hz), 3.21 (2H, t, J=7.3 Hz), 2.82 (2H, q, J=7.6 Hz), 2.68 (3H, s), 1.38 (3H, t, J=7.6 Hz).

STEP 6. 1-{1-[4-(2-Azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}ethanone

20 The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-{1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}ethanone (step 5).

25 ¹H-NMR (CDCl₃) δ 8.40 (1H, d, J=1.5 Hz), 7.90 (1H, dd, J=1.5 Hz, 8.6 Hz), 7.46 (2H, d, J=8.3 Hz), 7.12 (2H, d, J=8.3 Hz), 7.02 (1H, d, J=8.6 Hz), 3.63 (2H, t, J=6.9 Hz), 3.03 (2H, t, J=6.9 Hz), 2.80 (2H, q, J=7.4 Hz), 2.67 (3H, s), 1.37 (3H, t, J=7.4 Hz).

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STEP 7. 1-{1-[4-(2-Aminoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}ethanone

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-{1-[4-(2-azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}ethanone (step 6).

¹H-NMR (CDCl₃) δ 8.40 (1H, d, J=1.7 Hz), 7.90 (1H, dd, J=1.7 Hz, 8.6 Hz), 7.43 (2H, d, J=8.2 Hz), 7.30 (2H, d, J=8.2 Hz), 7.13 (1H, d, J=8.6 Hz), 3.08 (2H, t, J=6.7 Hz), 2.88 (2H, t, J=6.7 Hz), 2.80 (2H, q, J=7.6 Hz), 2.68 (3H, s), 1.38 (3H, t, J=7.6 Hz).

STEP 8. 5-Acetyl-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-{1-[4-(2-aminoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}ethanone (step 7).

MS (ESI) *m/z* 505 (M + H)⁺; ¹H-NMR CDCl₃) δ 8.40 (1H, d, J=1.1 Hz), 7.88 (1H, dd, J=1.1 Hz, 8.6 Hz), 7.73 (2H, d, J=8.4 Hz), 7.40 (2H, d, J=8.4 Hz), 7.27-7.31 (4H, m), 7.10 (1H, d, J=8.6 Hz), 6.74 (1H, br.s), 3.59 (2H, t, J=6.9 Hz), 2.95 (2H, t, J=6.9 Hz), 2.80 (2H, q, J=7.6 Hz), 2.67 (3H, s), 2.40 (3H, s), 1.36 (3H, t, J=7.6 Hz).

EXAMPLE 79

5-ACETYL-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 5-acetyl-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)

amino]ethyl}phenyl)-1*H*-benzimidazole (Example 78).

mp 155-160 °C; ¹H-NMR (DMSO-d₆) δ 8.32 (1H, d, J=1.6 Hz), 7.81 (1H, dd, J=1.6 Hz, 8.6 Hz), 7.62 (2H, d, J=8.1 Hz), 7.42 (4H, s), 7.12-7.17 (3H, m), 3.18 (2H, br.s), 2.71-2.79 (4H, m), 2.63 (3H, s), 2.27 (3H, s), 1.25 (3H, t, J=7.4 Hz);

IR (KBr) ν_{max} 3373, 1676, 1604, 1519, 1294, 1130, 1085, 885, 813 cm⁻¹.

EXAMPLE 80

2-ETHYL-5-METHYLSULFONYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL)PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-{4-[4-(Methylsulfonyl)-2-nitroanilino]phenyl}ethanol

A mixture of 2-chloro-5-methylsulfonylnitrobenzene (Kavalek, J.; et al. *Collect. Czech. Chem. Commun.*, 1971, 36, 209., 2 g, 8.5 mmol), 4-aminophenylethyl alcohol (1.4 g, 10.2 mmol) and Na₂CO₃ (1.4 g, 12.7 mmol) in ethanol was stirred at 100 °C for 16 h. The insoluble matter was removed by filtration and washed with ethanol (100 mL). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:4) to afford 960 mg (34%) of the title compound as yellow solids: ¹H-NMR (CDCl₃) δ 9.84 (1H, br.s), 8.82 (1H, d, J=2.1 Hz), 7.79 (1H, dd, J=2.1 Hz, 9.1 Hz), 7.36 (2H, d, J=8.4 Hz), 7.22-7.38 (3H, m), 3.94 (2H, br.s), 3.07 (3H, s), 2.93 (2H, t, J=6.6 Hz).

STEP 2. 2-{4-[2-Amino-4-(methylsulfonyl)anilino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[4-(methylsulfonyl)-2-nitroanilino]phenyl}ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.31 (1H, s), 7.28 (1H, s), 7.16-7.21 (3H, m), 6.96 (2H, d, J=8.5 Hz), 5.56 (1H, br.s), 3.86 (2H, t, J=6.4 Hz), 3.76 (2H, br.s), 3.03 (3H, s), 2.84 (2H, t, J=6.4 Hz).

STEP 3. 2-{4-[2-Ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[2-amino-4-(methylsulfonyl)anilino]phenyl} ethanol

5 (step 2) and propionyl chloride.

TLC R_f = 0.8 (dichloromethane/methanol = 10:1).

STEP 4. 2-{4-[2-Ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 8.38 (1H, d, J=1.4 Hz), 7.77 (1H, dd, J=1.4 Hz, 8.6 Hz), 7.50 (2H, d, J=8.4 Hz), 7.24-7.32 (2H, m), 7.22 (1H, d, J=8.6 Hz), 4.01 (t, J=6.6 Hz), 3.08 (3H, s), 3.02 (2H, t, J=6.6 Hz), 2.82 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz).

STEP 5. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-5-(methylsulfonyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-{4-[2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethanol (step 4).

¹H-NMR (CDCl₃) δ 8.38 (1H, d, J=1.6 Hz), 7.78 (1H, d, J=1.6 Hz, 8.6 Hz), 7.49 (2H, d, J=8.1 Hz), 7.32 (2H, d, J=8.1 Hz), 7.23 (1H, d, J=8.6 Hz), 3.84 (2H, t, J=6.9 Hz), 3.22 (2H, t, J=6.9 Hz), 3.08 (3H, s), 2.82 (2H, q, J=7.5 Hz), 1.38 (3H, t, J=7.5 Hz).

STEP 6. 1-[4-(2-Azidoethyl)phenyl]-2-ethyl-1H-benzimidazol-5-yl methyl sulfone

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-5-(methylsulfonyl)-1*H*-benzimidazole (step 5).

¹H-NMR (CDCl₃) δ 8.38 (1H, d, J=1.5 Hz), 7.78 (1H, dd, J=1.5 Hz, 8.6 Hz), 7.49 (2H, d, J=8.4 Hz), 7.32 (2H, d, J=8.4 Hz), 7.21 (1H, d, J=8.6 Hz), 3.64 (2H, t, J=6.9 Hz), 3.08 (3H, s), 3.03 (2H, t, J=6.9 Hz), 2.83 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz).

STEP 7. 2-{4-[2-Ethyl-5-(methylsulfonyl)-1*H*-benzimidazol-5-yl]phenyl}ethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl methyl sulfone (step 6).

¹H-NMR (CDCl₃) δ 8.38 (1H, d, J=1.7 Hz), 7.77 (1H, dd, J=1.7 Hz, 8.6 Hz), 7.46 (2H, d, J=8.4 Hz), 7.21-7.30 (3H, m), 3.03-3.08 (5H, m), 2.89 (2H, t, J=6.7 Hz), 2.82 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz).

STEP 8. 2-Ethyl-5-(methylsulfonyl)-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-{4-[2-ethyl-5-(methylsulfonyl)-1*H*-benzimidazol-5-yl]phenyl}ethylamine (step 7).

¹H-NMR (CDCl₃) δ 8.37 (1H, d, J=1.6 Hz), 7.75 (1H, dd, J=1.6 Hz, 8.6 Hz), 7.74 (2H, d, J=8.4 Hz), 7.43 (2H, d, J=8.2 Hz), 7.27-7.32 (4H, m), 7.18 (1H, d, J=8.6 Hz), 6.70 (1H, br.s), 3.59 (2H, t, J=6.8 Hz), 3.08 (3H, s), 2.96 (2H, t, J=6.8 Hz), 2.82 (2H, q, J=7.6 Hz), 2.41 (3H, s), 1.35 (4H, t, J=7.6 Hz).

EXAMPLE 81

2-ETHYL-5-METHYLSULFONYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in

- 5 Example 2 from 2-ethyl-5-(methylsulfonyl)-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino}ethyl}phenyl)-1H-benzimidazole (Example 80).

mp 171-178 °C; ¹H-NMR (DMSO-d₆) δ 8.08 (1H, br.s), 7.51-7.62 (3H, m), 7.32 (4H, s), 7.16 (1H, d, J=8.6 Hz), 7.03 (2H, d, J=7.3 Hz), 3.09-3.25 (7H, m), 2.63-
10 2.66 (2H, m), 2.16 (3H, s), 1.13 (3H, t, J=7.3 Hz); IR (KBr) ν_{max} 3386, 1604, 1519, 1396, 1299, 1128, 1085, 962, 887 cm⁻¹.

EXAMPLE 82

5-CYANO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2-[(4-Cyano-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 4-chloro-3-nitrobenzonitrile and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.80 (1H, br.s), 8.54 (1H, d, J=2.0 Hz), 7.50 (1H, dd, J=9.1, 2.0 Hz), 7.36 (2H, d, J=8.4Hz), 7.23 (2H, d, J=8.4 Hz), 7.16 (1H, d, J=9.1 Hz),
20 3.94-3.91 (2H, m), 2.93 (2H, t, J=6.6 Hz), 1.81 (1H, m).

STEP 2. 2-[(2-Amino-4-cyanoanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[(4-cyano-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.18-7.10 (3H, m), 7.01-6.95 (4H, m), 6.09 (1H, m), 3.97 (2H, br.s), 3.83-3.82 (2H, m), 2.83 (2H, t, J=6.8 Hz), 2.31 (1H, m)

STEP 3. 2-[4-(5-Cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

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The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-4-cyanoanilino)phenyl]ethanol (step 2).

MS (EI) m/z 347 (M^+).

STEP 4. 2-[4-(5-Cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol

- 5 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5-cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

$^1\text{H-NMR}$ (CDCl_3) δ 8.09 (1H, s), 7.50-7.43 (3H, m), 7.32-7.28 (2H, m), 7.15 (1H, d, $J=8.2$ Hz), 4.00 (2H, q, $H=6.4$ Hz), 3.01 (2H, t, $J=6.4$ Hz), 2.81 (2H, t, $J=7.6$ Hz), 1.37 (3H, t, $J=7.6$ Hz).

STEP 5. 2-[4-(5-Cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(5-cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

- 15 TLC R_f = 0.83 (dichloromethane/methanol = 10:1).

STEP 6. 2-[4-(5-Cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(5-cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

- 20 $^1\text{H-NMR}$ (CDCl_3) δ 8.09 (1H, s), 7.47-7.42 (3H, m), 7.29-7.26 (2H, m), 7.15 (1H, d, $J=8.4$ Hz), 3.09 (2H, t, $J=6.8$ Hz), 2.91 (2H, t, $J=6.8$ Hz), 2.81 (2H, q, $J=7.6$ Hz), 1.37 (3H, t, $J=7.6$ Hz).

STEP 7. 5-Cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino]ethyl]-1H-benzimidazole

- 25 benzimidazole

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The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(5-cyano-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 8.05 (1H, d, J=0.9 Hz), 7.75 (2H, d, J=8.4 Hz), 7.43-7.40 (3H, m), 7.30-7.26 (4H, m), 7.12 (1H, d, J=8.4 Hz), 6.74 (1H, m), 3.60-3.58 (2H, m), 2.96 (2H, t, J=7.0 Hz), 2.81 (2H, q, J=7.5 Hz), 2.41 (3H, s), 1.34 (3H, t, J=7.5 Hz).

EXAMPLE 83

5-CYANO-2-ETHYL-1-(4-{2-[(4-

METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 5-cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole (Example 82).

¹H-NMR (DMSO-d₆) δ 8.19 (1H, d, J=1.5 Hz), 7.59 (2H, d, J=7.9 Hz), 7.54 (1H, dd, J=8.4, 1.5 Hz), 7.41 (4H, s), 7.23 (1H, d, J=8.4 Hz), 7.11 (2H, d, J=7.9 Hz), 3.14 (2H, m), 2.78-2.70 (4H, m), 2.26 (3H, s), 1.24 (3H, t, J=7.4 Hz).

EXAMPLE 84

2-ETHYL-1-(4-{2-[(4-

METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-1*H*-BENZIMIDAZOLE-5-CARBOXAMIDE

STEP 1. 2-Ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazole-5-
carboxamide

To a mixture of 2-[4-(5-cyano-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 4 of Example 82, 200 mg, 0.68 mmol), DMSO (0.06 mL, 0.82 mmol) and methanol (10 mL) was added 30% aqueous solution of hydrogen peroxide (0.12

mL, 1.0 mmol) and 0.2 M aqueous NaOH (0.06 mL). The mixture was stirred at 50 °C for 4 h, then cooled. The mixture was poured into water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with 2N aqueous NaOH (50 mL) and brine (50 mL), then dried (Na₂SO₄), and

concentrated to afford the title compound as pale yellow solids: ¹H-NMR (CDCl₃) δ 8.23 (1H, d, J=1.1 Hz), 7.96 (1H, br.s), 7.76 (1H, dd, J=1.1 Hz, 8.4 Hz), 7.42-7.51 (4H, m), 7.25 (1H, br.s), 7.09 (1H, d, J=8.4 Hz), 3.70 (2H, t, J=6.6 Hz), 2.85 (2H, t, J=6.9 Hz), 2.76 (2H, q, J=7.4 Hz), 1.24 (3H, t, J=7.4 Hz).

STEP 2. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazole-5-carboxamide (step 1).

¹H-NMR (CDCl₃) δ 8.17 (1H, d, J=1.7 Hz), 7.79 (1H, dd, J=1.7 Hz, 8.5 Hz), 7.46 (2H, d, J=8.3 Hz), 7.33 (2H, d, J=8.3 Hz), 7.15 (1H, d, J=8.5 Hz), 3.83 (2H, t, J=7.0 Hz), 3.21 (2H, t, J=7.0 Hz), 2.82 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz).

STEP 3. 1-[4-(2-Azidoethyl)phenyl]-2-ethyl-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-5-carboxamide (step 2).

¹H-NMR (CDCl₃) δ 8.17 (1H, d, J=1.5 Hz), 7.78 (1H, dd, J=1.5 Hz, 8.4 Hz), 7.46 (2H, d, J=8.2 Hz), 7.32 (2H, d, J=8.2 Hz), 7.13 (1H, d, J=8.4 Hz), 3.62 (2H, t, J=6.8 Hz), 3.03 (2H, t, J=6.8 Hz), 2.81 (2H, q, J=7.5 Hz), 1.36 (3H, t, J=7.5 Hz).

STEP 4. 1-[4-(2-Aminoethyl)phenyl]-2-ethyl-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 9 of Example 1 from 1-[4-(2-azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazole-5-carboxamide (step 3).

¹H-NMR (CDCl₃) δ 8.21 (1H, d, J=1.5 Hz), 7.79 (1H, dd, J=1.5 Hz, 8.4 Hz), 7.43 (2H, d, J=8.2 Hz), 7.28-7.31 (2H, m), 7.13 (1H, d, J=8.4 Hz), 3.05 (2H, t, J=6.7 Hz), 2.88 (2H, t, J=6.7 Hz), 2.81 (2H, q, J=7.6 Hz), 1.35 (3H, t, J=7.6 Hz).

STEP 5. 2-Ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-2-ethyl-1*H*-benzimidazole-5-carboxamide (step 4).

MS (ESI) *m/z* 506 (M + H)⁺; ¹H-NMR (CD₃OD) δ 8.13 (1H, s), 7.65-7.73 (3H, m), 7.32 (2H, d, J=8.2 Hz), 7.16-7.21 (4H, m), 7.00 (1H, d, J=8.6 Hz), 3.31 (2H, t, J=6.9 Hz), 2.75 (2H, t, J=6.9 Hz), 2.69 (2H, q, J=7.6 Hz), 2.21 (3H, s), 1.48 (3H, t, J=7.6 Hz).

EXAMPLE 85

6-CYANO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 3-[4-(2-Hydroxyethyl)anilino]-4-nitrobenzonitrile

The title compound was prepared according to the procedure described in step 3 of Example 1 from 3-chloro-4-nitrobenzonitrile (Tsuiji, K. *Chem. Pharm. Bull.* 1992, 40, 2399) and 4-aminophenylethyl alcohol..

MS (EI) *m/z* 383 (M⁺).

STEP 2. 3-[4-(2-Chloroethyl)anilino]-4-nitrobenzonitrile

The title compound was prepared according to the procedure described in step 7 Example 1 from 3-[4-(2-hydroxyethyl)anilino]-4-nitrobenzonitrile (step 1).

¹H-NMR (CDCl₃) δ 9.46 (1H, br.s), 8.29 (1H, d, J=8.8 Hz), 7.42 (1H, d, J=1.7 Hz), 7.35 (2H, d, J=8.3 Hz), 7.22 (2H, d, J=8.3 Hz), 6.97 (1H, dd, J=8.8, 1.7 Hz), 3.77 (2H, t, J=7.2 Hz), 3.13 (2H, t, J=7).

STEP 3. 4-Amino-3-[4-(2-chloroethyl)anilino]benzonitrile

- 5 The title compound was prepared according to the procedure described in step 4 of Example 1 from 3-[4-(2-chloroethyl)anilino]-4-nitrobenzonitrile (step 2).
MS (EI) m/z 383 (M⁺).

STEP 4. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-6-carbonitrile

- 10 The title compound was prepared according to the procedure described in step 5 of Example 1 from 4-amino-3-[4-(2-chloroethyl)anilino]benzonitrile (step 3) and propionyl chloride.
MS (EI) m/z 309 (M⁺); ¹H-NMR (CDCl₃) δ 7.82 (1H, d, J=8.6 Hz), 7.53 (1H, dd, J=8.6, 2.0 Hz), 7.48 (2H, d, J=8.3 Hz), 7.42 (1H, d, J=2.0 Hz), 7.31 (2H, d, J=8.3 Hz), 3.84 (2H, t, J=7.0 Hz), 3.21 (2H, t, J=7.0 Hz), 2.82 (2H, q, J=7.4 Hz),
15 1.39 (3H, t, J=7.4 Hz).

STEP 5. 2-[4-(6-Cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

- The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-6-carbonitrile (step 4).
20 MS (EI) m/z 316 (M⁺); ¹H-NMR (CDCl₃) δ 7.83 (1H, d, J=8.4 Hz), 7.54 (1H, dd, J=8.4, 2.0 Hz), 7.50 (2H, d, J=8.3 Hz), 7.40 (1H, d, J=2.0 Hz), 7.30 (2H, d, J=8.3 Hz), 3.64 (2H, t, J=6.5 Hz), 3.04 (2H, t, J=6.5 Hz), 2.83 (2H, q, J=7.3 Hz), 1.37 (3H, t, J=7.3 Hz).

- 25 STEP 6. 2-[4-(6-Cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

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The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(6-cyano-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

¹H-NMR (DMSO-*d*₆) δ 8.11 (2H, br.s), 7.87 (1H, d, J=8.4 Hz), 7.64 (1H, dd, J=8.4, 2.0 Hz), 7.60-7.53 (5H, m), 3.20-3.02 (4H, m), 2.79 (2H, q, J=7.4 Hz), 1.28 (3H, t, J=7.4 Hz).

STEP 7. 6-Cyano-2-ethyl-1-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl]amino]ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(6-cyano-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 7.83 (1H, d, J=8.4 Hz), 7.74 (2H, d, J=8.4 Hz), 7.53 (1H, dd, J=8.4, 1.5 Hz), 7.43 (2H, d, J=8.4 Hz), 7.39 (1H, d, J=1.5 Hz), 7.33 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 6.75 (1H, br.s), 3.65-3.54 (2H, m), 2.97 (2H, t, J=7.0 Hz), 2.82 (2H, q, J=7.5 Hz), 2.42 (3H, s), 1.37 (3H, t, J=7.5 Hz).

EXAMPLE 86

2-ETHYL-1-(4-{2-[(4-

METHYLPHENYL)SULFONYL]AMINO}CARBONYL]AMINO]ETHYL}PH
ENYL)-1*H*-BENZIMIDAZOLE-6-CARBOXAMIDE

To a solution of 6-cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl]amino]ethyl}phenyl)-1*H*-benzimidazole (Example 85, 162 mg, 0.33 mmol) in 2-methyl-2-propanol (10 mL) was added powdered KOH (66 mg, 1.0 mmol). The resulting mixture was heated at reflux temperature for 3 h. After removal of solvent, the reaction mixture was partitioned between dichloromethane (50 mL) and phosphate buffer (50 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (50 mL). The combined organic phases were washed with

brine (50 mL), dried (Na₂SO₄), and concentrated. The residual solids were recrystallized from ethyl acetate to afford 105 mg (63%) of the title compound as white solids: ¹H-NMR (CDCl₃) δ: 7.79 (2H, d, J=8.4 Hz), 7.75 (1H, d, J=8.8 Hz), 7.71-7.63 (2H, m), 7.35-7.25 (4H, m), 7.16 (2H, d, J=8.4 Hz), 6.75 (2H, br.s), 6.55 (1H, br.s), 3.54 (2H, t, J=6.4 Hz), 2.88 (2H, t, J=6.4 Hz), 2.79 (2H, q, J=7.5 Hz), 2.40 (3H, s), 1.34 (3H, t, J=7.5 Hz).

EXAMPLE 87

5-[(*tert*-BUTYLAMINO)SULFONYL]-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. *N*-(*tert*-Butyl)-4-chloro-3-nitrobenzenesulfonamide

To a stirred solution of *tert*-butylamine (5.1 g, 70 mmol) in dichloromethane (200 mL) was added dropwise a solution of 4-chloro-3-nitrobenzenesulfonyl chloride (17.9 g, 70 mmol) in dichloromethane (100 mL) at room temperature over a period of 30 min, and then the reaction mixture was stirred for 2 h. The reaction mixture was poured into water (100 mL), the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (100 mL). The combined organic extracts were washed with water (50 mL) and brine (20 mL), dried (Na₂SO₄), and concentrated to give 21.3 g (quant.) of the title

compound as yellow solids: ¹H-NMR (CDCl₃) δ 8.38 (1H, d, J=2.0 Hz), 8.02 (1H, dd, J=2.0, 8.6 Hz), 7.70 (1H, d, J=8.6 Hz), 4.95 (1H, br.s), 1.28 (9H, s).

STEP 2. *N*-(*tert*-Butyl)-4-[4-(2-hydroxyethyl)anilino]-3-nitrobenzenesulfonamide

The title compound was prepared according to the procedure described in step 3 of Example 1 from *N*-(*tert*-butyl)-4-chloro-3-nitrobenzenesulfonamide (step 1) and 4-aminophenylethyl alcohol.

MS (EI) m/z 393 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 9.76 (1H, br.s), 8.75 (1H, d, $J=2.0$ Hz), 7.74 (1H, dd, $J=2.0$, 8.5 Hz), 7.35 (2H, d, $J=8.3$ Hz), 7.24 (2H, d, $J=8.3$ Hz), 7.17 (1H, d, $J=8.5$ Hz), 4.42 (1H, br.s), 3.97-3.88 (2H, m), 2.94 (2H, t, $J=7.0$ Hz), 1.27 (9H, s).

5 STEP 3. *N*-(*tert*-Butyl)-4-[4-(2-chloroethyl)anilino]-3-nitrobenzenesulfonamide

The title compound was prepared according to the procedure described in step 7 Example 1 from *N*-(*tert*-butyl)-4-[4-(2-hydroxyethyl)anilino]-3-nitrobenzenesulfonamide (step 2).

10 MS (EI) m/z 411 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 9.77 (1H, br.s), 8.77 (1H, d, $J=2.0$ Hz), 7.77 (1H, dd, $J=2.0$, 8.4 Hz), 7.34 (2H, d, $J=8.3$ Hz), 7.25 (2H, d, $J=8.3$ Hz), 7.18 (1H, d, $J=8.4$ Hz), 4.46 (1H, br.s), 3.76 (2H, t, $J=6.8$ Hz), 3.13 (2H, t, $J=6.8$ Hz), 1.28 (9H, s).

STEP 4. 3-Amino-*N*-(*tert*-butyl)-4-[4-(2-chloroethyl)anilino]benzenesulfonamide

15 The title compound was prepared according to the procedure described in step 4 of Example 1 from *N*-(*tert*-butyl)-4-[4-(2-chloroethyl)anilino]-3-nitrobenzenesulfonamide (step 3).

$^1\text{H-NMR}$ (CDCl_3) δ 7.31 (1H, d, $J=2.0$ Hz), 7.26 (1H, dd, $J=2.0$, 8.3 Hz), 7.15 (1H, d, $J=8.3$ Hz), 7.14 (2H, d, $J=8.4$ Hz), 6.89 (2H, d, $J=8.4$ Hz), 5.49 (1H, br.s), 4.64 (1H, br.s), 3.77 (2H, br.s), 3.69 (2H, t, $J=7.4$ Hz), 3.02 (2H, t, $J=7.4$ Hz), 1.24 (9H, s).

20 STEP 5. *N*-(*tert*-Butyl)-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazole-5-sulfonamide

The title compound was prepared according to the procedure described in step 5 Example 1 from 3-amino-*N*-(*tert*-butyl)-4-[4-(2-chloroethyl)anilino]benzenesulfonamide (step 4) and propionyl chloride.

MS (EI) m/z 419 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 8.34 (1H, d, $J=2.0$ Hz), 7.74 (1H, dd, $J=2.0, 8.3$ Hz), 7.47 (2H, d, $J=8.6$ Hz), 7.33 (2H, d, $J=8.6$ Hz), 7.16 (1H, d, $J=8.3$ Hz), 4.62 (1H, br.s), 3.83 (2H, t, $J=7.0$ Hz), 3.21 (2H, t, $J=7.0$ Hz), 2.82 (2H, q, $J=7.4$ Hz), 1.39 (3H, t, $J=7.4$ Hz) 1.24 (9H, s).

5 STEP 6. 1-[4-(2-Azidoethyl)phenyl]-*N*-(*tert*-butyl)-2-ethyl-1*H*-benzimidazole-5-sulfonamide

The title compound was prepared according to the procedure described in step 8 of Example 1 from *N*-(*tert*-butyl)-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazole-5-sulfonamide (step 5).

10 MS (EI) m/z 426 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 8.33 (1H, d, $J=2.0$ Hz), 7.73 (1H, dd, $J=2.0, 8.4$ Hz), 7.48 (2H, d, $J=8.4$ Hz), 7.33 (2H, d, $J=8.4$ Hz), 7.14 (1H, d, $J=8.4$ Hz), 4.47 (1H, br.s), 3.62 (2H, t, $J=7.0$ Hz), 3.03 (2H, t, $J=7.0$ Hz), 2.82 (2H, q, $J=7.2$ Hz), 1.38 (3H, t, $J=7.2$ Hz) 1.24 (9H, s).

15 STEP 7. 1-[4-(2-Aminoethyl)phenyl]-*N*-(*tert*-butyl)-2-ethyl-1*H*-benzimidazole-5-sulfonamide

The title compound was prepared according to the procedure described in step 9 of Example 1 from 1-[4-(2-azidoethyl)phenyl]-*N*-(*tert*-butyl)-2-ethyl-1*H*-benzimidazole-5-sulfonamide (step 6).

$^1\text{H-NMR}$ (CDCl_3) δ 8.34 (1H, d, $J=1.9$ Hz), 7.74 (1H, dd, $J=1.9, 8.3$ Hz), 7.44 (2H, d, $J=8.4$ Hz), 7.28 (2H, d, $J=8.4$ Hz), 7.15 (1H, d, $J=8.3$ Hz), 4.88 (1H, br.s), 3.09 (2H, t, $J=7.0$ Hz), 2.95 (2H, t, $J=7.0$ Hz), 2.83 (2H, q, $J=7.4$ Hz), 1.37 (3H, t, $J=7.4$ Hz) 1.23 (9H, s).

25 STEP 8. 5-[(*tert*-Butylamino)sulfonyl]-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl]phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-*N*-(*tert*-butyl)-2-ethyl-1*H*-benzimidazole-5-sulfonamide (step 7).

09977761.301501

MS (ESI) m/z 598 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 8.32 (1H, d, J=1.3 Hz), 7.77-7.69 (3H, m), 7.41(2H, d, J=8.3 Hz), 7.33-7.25 (4H, m), 7.11 (1H, d, J=8.6 Hz), 6.65 (1H, br.s), 4.59 (1H, s), 3.63-3.53 (2H, m), 2.95 (2H, t, J=7.0 Hz), 2.80 (2H, q, J=7.6 Hz), 2.41 (3H, s), 1.36 (3H, t, J=7.6 Hz) 1.23 (9H, s).

5 EXAMPLE 88

5-(AMINOSULFONYL)-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

A solution of 5-[(*tert*-butylamino)sulfonyl]-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole (Example 87, 330 mg, 0.55 mmol) in trifluoroacetic acid (10 mL) was heated at 80 °C for 2 h. The mixture was concentrated and the residue was purified by flash chromatography on silica gel eluting with dichloromethane/methanol (10:1) to afford 215 mg (73%) of the title compound: MS (ESI) m/z 542 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 8.32 (1H, d, J=1.3 Hz), 7.77-7.69 (3H, m), 7.41(2H, d, J=8.3 Hz), 7.33-7.25 (4H, m), 7.11 (1H, d, J=8.6 Hz), 6.65 (1H, br.s), 4.59 (1H, s), 3.63-3.53 (2H, m), 2.95 (2H, t, J=7.0 Hz), 2.80 (2H, q, J=7.6 Hz), 2.41 (3H, s), 1.36 (3H, t, J=7.6 Hz) 1.23 (9H, s).

15 EXAMPLE 89

2-ETHYL-1-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}-5-[(METHYL SULFONYL)AMINO]-1H-BENZIMIDAZOLE

STEP 1. 2-[4-(2,4-Dinitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-chloro-1,5-dinitrobenzene and 4-aminophenylethyl alcohol.

0977751.101501

¹H-NMR (CDCl₃) δ 9.95 (1H, s), 9.18 (1H, d, J=2.4 Hz), 8.16 (1H, dd, J=2.7, 9.7 Hz), 7.39 (2H, d, J=8.4 Hz), 7.26 (2H, d, J=8.1 Hz), 7.16 (1H, d, J=9.5 Hz), 3.93 (2H, dt, J=5.7, 6.2 Hz), 2.94 (2H, t, J=6.8 Hz), 1.50 (1H, t, J=5.7 Hz).

STEP 2. 2-[4-(2-Amino-4-nitroanilino)phenyl]ethanol

- 5 The title compound was prepared according to the procedure described in step 2 of Example 40 from 2-[4-(2,4-dinitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.73-7.67 (2H, m), 7.22 (2H, d, J=8.3 Hz), 7.11 (1H, d, J=9.3 Hz), 7.04 (2H, d, J=8.3 Hz), 5.80 (1H, s), 3.88 (2H, dt, J=5.7, 6.0 Hz), 3.69 (2H, br.s), 2.87 (2H, t, J=6.4 Hz), 1.48 (1H, br).

- 10 STEP 3. 2-[4-(2-ethyl-5-nitro-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-4-nitroanilino)phenyl]ethanol (step 2) and propionyl chloride.

- 15 ¹H-NMR (CDCl₃) δ 8.68 (1H, d, J=2.2 Hz), 8.13 (1H, dd, J=2.2, 9.0 Hz), 7.48 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=8.3 Hz), 7.13 (1H, d, J=8.97 Hz), 4.39 (2H, t, J=6.8 Hz), 3.09 (2H, t, J=7.0 Hz), 2.81 (2H, q, J=7.5 Hz), 2.36 (2H, q, J=7.5 Hz), 1.38 (3H, t, J=7.5 Hz), 1.15 (3H, q, J=7.5 Hz).

STEP 4. 2-[4-(5-Amino-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

- 20 To a stirred solution of 2-[4-(2-ethyl-5-nitro-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3, 1.12 g, 3.0 mmol) in ethanol/water (v/v, 2:1, 15 mL) was added ammonium chloride (80 mg, 1.5 mmol) and iron powder (840 mg, 15 mmol) at room temperature. The mixture was heated at reflux temperature for 4 h and filtered through a pad of Celite. The filtrate was concentrated, and the residue was dissolved in dichloromethane (200 mL), then dried (MgSO₄).
- 25 Removal of solvent gave 0.84 g (83%) of the title compound as a yellow oil: ¹H-NMR (CDCl₃) δ 7.41 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.6 Hz), 7.10 (1H, d,

J=1.8 Hz), 6.89 (1H, d, J=8.4 Hz), 6.63 (1H, dd, J=2.2, 8.4 Hz), 4.37 (2H, t, J=7.0 Hz), 3.05 (2H, t, J=7.1 Hz), 2.79 (2H, q, J=7.5 Hz), 2.35 (2H, q, J=7.5 Hz), 1.33 (3H, t, J=7.5 Hz), 1.14 (3H, t, J=7.7 Hz).

STEP 5. 2-(4-{2-Ethyl-5-[(methylsulfonyl)amino]-1H-benzimidazol-1-

yl}phenyl)ethyl propionate

To a stirred solution of 2-[4-(5-amino-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 4, 1.18 g, 3.50 mmol) in dichloromethane (20 mL) was added methanesulfonyl chloride (0.40 mL, 5.25 mmol) and pyridine (0.42 mL, 5.25 mmol) at room temperature. After stirring for 6h, the mixture

was poured into 10% aqueous citric acid (100 mL) and extracted with ethyl acetate (100 mL). The aqueous layer was made basic with saturated aqueous sodium bicarbonate (100 mL) and extracted with ethyl acetate (100 mL). The combined organic extracts were washed with brine (100 mL) and dried (MgSO₄), and concentrated to afford 1.28 g (88%) of the title compound as

brown amorphous: ¹H-NMR (CDCl₃) δ 8.47 (1H, s), 7.66 (1H, d, J=1.7 Hz), 7.50 (2H, d, J=8.4 Hz), 7.42 (1H, dd, J=2.0, 8.8 Hz), 7.41 (2H, d, J=8.4 Hz), 7.09 (1H, d, J=8.8 Hz), 4.39 (2H, t, J=7.0 Hz), 3.09 (2H, t, J=6.8 Hz), 3.00 (2H, q, J=7.7 Hz), 2.36 (2H, q, J=7.7 Hz), 1.42 (3H, t, J=7.7 Hz), 1.15 (3H, t, J=7.5 Hz).

STEP 6. 2-Ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazol-5-

yl}methanesulfonamide

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-(4-{2-ethyl-5-[(methylsulfonyl)amino]-1H-benzimidazol-1-yl}phenyl)ethyl propionate (step 5).

¹H-NMR (CDCl₃) δ 7.63 (1H, d, J=1.8 Hz), 7.46 (2H, d, J=8.2 Hz), 7.29 (2H, d, J=8.4 Hz), 7.18 (1H, dd, J=2.1, 8.6 Hz), 7.07 (1H, d, J=8.6 Hz), 6.68 (1H, br), 3.99 (2H, t, J=6.4 Hz), 3.01 (2H, t, J=6.8 Hz), 2.98 (3H, s), 2.79 (2H, q, J=7.4 Hz), 1.35 (3H, t, J=7.6 Hz).

STEP 7. *N*-{1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazol-5-

yl}methanesulfonamide (step 6).

¹H-NMR (CDCl₃) δ 7.74-6.85 (7H, m), 3.83 (2H, t, J=7.1 Hz), 3.21 (2H, t, J=7.1 Hz), 2.98 (3H, s), 2.85 (2H, q, J=7.5 Hz), 1.38 (3H, t, J=7.5 Hz).

STEP 8. *N*-{1-[4-(2-Azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide

The title compound was prepared according to the procedure described in step 8 of Example 1 from *N*-{1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide (step 7).

¹H-NMR (CDCl₃) δ 7.64 (1H, br), 7.45 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=8.1 Hz), 7.19 (1H, dd, J=1.8, 8.8 Hz), 7.07 (1H, d, J=8.4 Hz), 6.81 (1H, s), 3.62 (2H, t, J=6.8 Hz), 3.02 (2H, t, J=7.0 Hz), 2.98 (3H, s), 2.79 (2H, q, J=7.5 Hz), 1.35 (3H, t, J=7.5 Hz).

STEP 9. *N*-{1-[4-(2-Aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide

The title compound was prepared according to the procedure described in step 9 of Example 1 from *N*-{1-[4-(2-azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide (step 8).

MS (EI) *m/z* 358 (M⁺).

STEP 10. *N*-{1-[4-(2-aminoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from *N*-{1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide (step 9).

MS (ESI) m/z 556 ($M + H$)⁺; ¹H-NMR (CDCl₃) δ 9.49 (1H, s), 7.76 (2H, d, $J=7.1$ Hz), 7.51 (1H, br), 7.42-7.34 (6H, m), 7.07 (1H, d, $J=8.6$ Hz), 7.01 (1H, d, $J=8.6$ Hz), 6.53 (1H, br), 3.40-3.33 (2H, m), 2.89 (3H, s), 2.81-2.66 (4H, m), 2.33 (3H, s), 1.21 (3H, t, $J=7.5$ Hz); IR (KBr) ν_{\max} 1697, 1684, 1508, 1458, 1148 cm⁻¹.

EXAMPLE 90

2-ETHYL-5-HYDROXY-1- (4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 1-[4-(2-Bromoethyl)phenyl]-2-ethyl-1H-benzimidazol-5-ol

A mixture of 1-[4-(2-chloroethyl)phenyl]-2-ethyl-5-methoxy-1H-benzimidazole (step 5 of Example 71, 600 mg, 1.9 mmol) in 48% hydrobromic acid (60 mL) was stirred at 100 °C for 6 h. After cooling, the mixture was neutralized with 2N aqueous NaOH and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (50 mL), dried (Na₂SO₄), and concentrated to afford 890 mg (quant.) of the title compound as pale yellow solids: ¹H-NMR (CDCl₃) δ 7.64 (4H, s), 7.16 (2H, m), 6.97-7.01 (1H, m), 3.86 (2H, t, $J=7.1$ Hz), 3.30 (2H, t, $J=7.1$ Hz), 2.92 (2H, q, $J=7.8$ Hz), 1.29 (3H, t, $J=7.8$ Hz).

STEP 2. 1-[4-(2-Bromoethyl)phenyl]-2-ethyl-1H-benzimidazol-5-yl tert-butyl(dimethyl)silyl ether

A mixture of 1-[4-(2-bromoethyl)phenyl]-2-ethyl-1H-benzimidazol-5-ol (step 1, 200 mg, 0.58 mmol), *tert*-butyldimethylsilyl chloride (100 mg, 0.7 mmol) and imidazole (47 mg, 1.45 mmol) in DMF (5 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (50 mL), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate

(1:1) to afford 119 mg (45%) of the title compound as white solids: $^1\text{H-NMR}$ (CDCl_3) δ 7.20 (2H, d, $J=8.4$ Hz), 7.10 (2H, d, $J=8.4$ Hz), 7.01 (1H, d, $J=2.3$ Hz), 6.72 (1H, d, $J=8.6$ Hz), 6.52 (1H, dd, $J=2.3$ Hz, 8.6 Hz), 3.45 (2H, t, $J=7.4$ Hz), 3.07 (2H, t, $J=7.4$ Hz), 2.56 (2H, q, $J=7.5$ Hz), 1.14 (3H, t, $J=7.5$ Hz), 0.79 (9H, s), 0.05 (6H, s).

STEP 3. 1-[4-(2-Azidoethyl)phenyl]-2-ethyl-1H-benzimidazol-5-yl tert-butyl(dimethyl)silyl ether

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-bromoethyl)phenyl]-2-ethyl-1H-benzimidazol-5-yl tert-butyl(dimethyl)silyl ether (step 2).

$^1\text{H-NMR}$ (CDCl_3) δ 7.20 (2H, d, $J=8.3$ Hz), 7.02-7.12 (3H, m), 6.70 (1H, d, $J=8.6$ Hz), 6.50-6.54 (1H, m), 3.39 (2H, t, $J=6.9$ Hz), 2.79 (2H, t, $J=6.9$ Hz), 2.55 (2H, q, $J=7.6$ Hz), 1.13 (3H, t, $J=7.6$ Hz), 0.79 (9H, s), 0.00 (6H, s).

STEP 4. 2-[4-(5-{[tert-Butyl(dimethyl)silyl]oxy}-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-2-ethyl-1H-benzimidazol-5-yl tert-butyl(dimethyl)silyl ether (step 3).

$^1\text{H-NMR}$ (CDCl_3) δ 7.18 (2H, d, $J=8.2$ Hz), 7.02-7.08 (3H, m), 6.72 (1H, d, $J=8.6$ Hz), 6.52 (1H, dd, $J=2.2$ Hz, 8.6 Hz), 2.86 (2H, t, $J=6.6$ Hz), 2.66 (2H, t, $J=6.6$ Hz), 2.55 (2H, q, $J=7.5$ Hz), 1.13 (3H, t, $J=7.5$ Hz), 0.79 (9H, s), 0.00 (6H, s).

STEP 5. 5-{[tert-Butyl(dimethyl)silyl]oxy}-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(5-{[tert-butyl(dimethyl)silyl]oxy}-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine (step 4).

¹H-NMR (CDCl₃) δ 7.53 (2H, d, J=8.3 Hz), 7.02-7.13 (7H, m), 6.70 (1H, d, J=8.6 Hz), 6.52 (1H, dd, J=2.2 Hz, 8.6 Hz), 6.46 (1H, br.s), 3.37 (2H, t, J=6.4 Hz), 2.71 (2H, t, J=6.4 Hz), 2.53 (2H, q, J=7.6 Hz), 2.18 (3H, s), 1.11 (3H, t, J=7.6 Hz), 0.79 (9H, s), 0.00 (6H, s).

5 STEP 6. 2-Ethyl-5-hydroxy-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole

A solution of 5-{*tert*-butyl(dimethyl)silyl]oxy}-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole (step 5, 78 mg, 0.13 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.16 mL, 0.16 mmol) at 0 °C. The mixture was stirred at 0 °C for 2.5 h, then concentrated. The residue was dissolved in water (30 mL) and extracted with dichloromethane (50 mL). The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol (gradient elution from 20:1 to 10:1) to afford 57 mg (92%) of the title compound as white amorphous: MS (ESI) m/z 479 (M + H)⁺; ¹H-NMR (DMSO-d₆) δ 7.76 (2H, d, J=7.6 Hz), 7.35-7.39 (6H, m), 6.96 (1H, s), 6.85 (1H, d, J=8.6 Hz), 6.65 (1H, d, J=8.6 Hz), 6.51 (1H, br.s), 3.17 (2H, br.s), 2.76 (2H, t, 6.6 Hz), 2.67 (2H, q, J=7.6 Hz), 2.34 (3H, s), 1.20 (3H, t, J=7.6 Hz).

20 EXAMPLE 91

2-ETHYL-4,5-DIMETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2-[(3,4-DIMETHYL-2-NITROANILINO)PHENYL]ETHANOL

25 The title compound was prepared according to the procedure described in step 1 of Example 45 from 3,4-dimethyl-2-nitroaniline and 4-bromophenylethyl ethanol.

¹H-NMR (CDCl₃) δ 7.16 (2H, d, J=8.4 Hz), 7.09 (1H, s), 7.03 (2H, d, J=8.4 Hz), 6.91 (1H, s), 3.89-3.81 (2H, m), 2.83 (2H, t, J=6.4 Hz), 2.27 (3H, s), 2.25 (3H, s)
STEP 2. 2-[(2-Amino-3,4-dimethylanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[(3,4-dimethyl-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.02 (2H, d, J=8.6 Hz), 6.86 (1H, d, J=7.9 Hz), 6.62-6.58 (3H, m), 5.09 (1H, br.s), 3.77 (2H, t, J=6.6 Hz), 2.74 (2H, t, J=6.6 Hz), 2.27 (3H, s), 2.11 (3H, s)

STEP 3. 2-[4-(2-Ethyl-4,5-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-3,4-dimethylanilino)phenyl]ethanol (step 2) and propionyl chloride.

MS (EI) m/z 350 (M⁺).

STEP 4. 2-[4-(2-Ethyl-4,5-dimethyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-4,5-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.4 Hz), 7.27 (2H, d, J=8.4 Hz), 6.99 (1H, d, J=8.3 Hz), 6.82 (1H, d, J=8.3 Hz), 3.98 (2H, t, J=6.6 Hz), 2.99 (2H, t, J=6.6 Hz), 2.82 (2H, q, J=7.5 Hz), 2.63 (3H, s), 2.39 (3H, s), 1.26 (3H, t, J=7.5 Hz).

STEP 5. 2-[4-(2-Ethyl-4,5-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(2-ethyl-4,5-dimethyl-1H-benzimidazol-1-

yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.6Hz), 7.30 (2H, d, J=8.6Hz), 7.00 (1H, d, J=8.2Hz), 6.82 (1H, d, J=8.2Hz), 3.61 (2H, t, J=7.1Hz), 3.01 (2H, t, J=7.1Hz), 2.83 (2H, q, J=7.6Hz), 2.63 (3H, s), 2.39 (3H, s), 1.26 (3H, t, J=7.6Hz).

STEP 6. 2-[4-(2-Ethyl-4,5-dimethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

- 5 The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-4,5-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 7.39 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 6.99 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.2 Hz), 3.09 (2H, t, J=6.6 Hz), 2.92-2.79 (4H, m),

- 10 2.63 (3H, s),
2.39 (3H, s), 1.27 (3H, t, J=7.6 Hz)

STEP 7. 2-Ethyl-4,5-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step

- 15 10 of Example 1 from 2-[4-(2-ethyl-4,5-dimethyl-1H-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 7.76 (2H, d, J=8.2 Hz), 7.30-7.19 (6H, m), 7.00 (1H, d, J=8.2 Hz), 6.81 (1H, d, J=8.2 Hz), 6.65 (1H, m), 3.56-3.54 (2H, m), 2.89 (2H, t, J=6.9 Hz), 2.80 (2H, q, J=7.6 Hz), 2.59 (3H, s), 2.38 (6H, s), 1.22 (3H, t, J=7.6 Hz).

- 20 Hz).

EXAMPLE 92

2-ETHYL-4,5-DIMETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

- 25 The title compound was prepared according to the procedure described in Example 2 from 2-ethyl-4,5-dimethyl-1-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole (Example 91).

¹H-NMR (DMSO-*d*₆) δ 7.59 (2H, d, *J*=8.4 Hz), 7.39-7.30 (4H, m), 7.12 (2H, d, *J*=8.4 Hz), 6.94 (1H, d, *J*=8.3 Hz), 6.77 (1H, d, *J*=8.3 Hz), 3.13 (2H, m), 2.74-2.67 (4H, m), 2.48 (3H, s), 2.30 (3H, s), 2.27 (3H, s), 1.19 (3H, t, *J*=7.5 Hz); IR (KBr) ν_{max} 1599, 1516, 1425, 1227, 1128, 1086 cm⁻¹.

EXAMPLE 93

4,6-DIMETHYL-2-ETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-[4-(3,5-Dimethyl-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 4,6-dimethyl-2-fluoronitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 8.08 (1H, br.s), 7.22 (2H, d, *J*=8.4 Hz), 7.13 (2H, d, *J*=8.4 Hz), 6.91 (1H, s), 6.51 (1H, s), 3.89 (2H, t, *J*=6.4 Hz), 2.87 (2H, t, *J*=6.4 Hz), 2.47 (3H, s), 2.22 (3H, s).

STEP 2. 2-[4-(2-Amino-3,5-dimethylanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 4 of Example 1 from 2-[4-(3,5-dimethyl-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 6.97-7.04 (2H, m), 6.78 (1H, s), 6.74 (1H, s), 6.59-6.67 (1H, s), 5.15 (1H, br.s), 3.76 (2H, t, *J*=6.6 Hz), 2.74 (2H, t, *J*=6.6 Hz), 2.18 (3H, s), 2.17 (3H, s).

STEP 3. 2-[4-(2-Ethyl-4,6-dimethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl

propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-3,5-dimethylanilino)phenyl]ethanol (step 2) and propionyl chloride.

TLC Rf = 0.7 (hexane/ethyl acetate = 1:1).

5 STEP 4. 2-[4-(2-Ethyl-4,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-amino-3,5-dimethylanilino)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.1 Hz), 7.27 (2H, d, J=8.1 Hz), 6.90 (1H, s), 6.71 (1H, s), 3.98 (2H, t, J=6.4 Hz), 2.99 (2H, t, J=6.4 Hz), 2.81 (2H, q, J=7.3 Hz), 2.65 (3H, s), 2.36 (3H, s), 1.24 (3H, t, J=7.3 Hz).

STEP 5. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-4,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.0 Hz), 7.30 (2H, d, J=8.0 Hz), 6.90 (1H, s), 6.71 (1H, s), 3.81 (2H, t, J=7.2 Hz), 3.19 (2H, t, J=7.2 Hz), 2.81 (2H, q, J=7.7 Hz), 2.67 (3H, s), 2.37 (3H, s), 1.25 (3H, t, J=7.7 Hz).

STEP 6. 2-[4-(2-Ethyl-4,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole (step 5).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.3 Hz), 6.90 (1H, s), 6.69 (1H, s), 3.62 (2H, t, J=7.0 Hz), 3.01 (2H, d, J=7.0 Hz), 2.81 (2H, q, J=7.5 Hz), 2.66 (3H, s), 2.36 (3H, s), 1.25 (3H, t, J=7.5 Hz).

STEP 7. 2-[4-(2-Ethyl-4,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-4,6-dimethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 6).

¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.2 Hz), 7.27 (2H, d, J=8.2 Hz), 6.89 (1H, s), 6.71 (1H, s), 3.07 (2H, t, J=6.9 Hz), 2.77-2.89 (4H, m), 2.67 (3H, s), 2.36 (3H, s), 1.25 (3H, t, J=7.6 Hz).

STEP 8. 2-Ethyl-4,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-4,6-dimethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 7).

mp 108-112 °C; MS (ESI) m/z 491 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.75 (2H, d, J=8.2 Hz), 7.18-7.29 (6H, m), 6.89 (1H, s), 6.67 (1H, s), 6.62 (1H, br.s), 3.51 (2H, br.s), 2.86 (2H, br.s), 2.76 (2H, q, J=7.4 Hz), 2.63 (3H, s), 2.37 (3H, s), 2.33 (3H, s), 1.20 (3H, t, J=7.4 Hz).

EXAMPLE 94

5,6-DIMETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 2-[(4,5-Dimethyl-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 1 of Example 45 from 4,5-dimethyl-2-nitroaniline and 4-bromophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.39 (1H, br.s), 7.96 (1H, s), 7.27 (2H, d, J=8.4 Hz), 7.21 (2H, d, J=8.4 Hz), 7.01 (1H, s), 3.91 (2H, q, J=6.4 Hz), 2.90 (2H, t, J=6.4 Hz), 2.20 (3H, s), 2.19 (3H, s).

STEP 2. 2-[(2-Amino-4,5-dimethylanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[(4,5-dimethyl-2-nitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.04 (2H, d, J=8.4 Hz), 6.86 (1H, s), 6.64 (2H, d, J=8.4 Hz), 6.61 (1H, s), 3.79 (2H, t, J=6.6 Hz), 2.76 (2H, t, J=6.6 Hz), 2.19 (3H, s), 2.12 (3H, s)

STEP 3. 2-[4-(2-Ethyl-5,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-4,5-dimethylanilino)phenyl]ethanol (step 2) and propionyl chloride.

MS (EI) m/z 350 (M⁺).

STEP 4. 2-[4-(2-Ethyl-5,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-ethyl-5,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.52 (1H, s), 7.44 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 6.87 (1H, s), 4.00 (2H, t, J=6.6 Hz), 3.01 (2H, t, J=6.6 Hz), 2.76 (2H, q, J=7.5 Hz), 2.36 (3H, s), 2.29 (3H, s), 1.31 (3H, t, J=7.5 Hz).

STEP 5. 2-[4-(2-Ethyl-5,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(2-ethyl-5,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

TLC Rf = 0.70 (hexane/ethyl acetate = 1:1).

STEP 6. 2-[4-(2-Ethyl-5,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-5,6-dimethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 7.53 (1H, s), 7.40 (2H, d, J=8.1 Hz), 7.28 (2H, d, J=8.1 Hz), 6.87 (1H, s), 3.17 (2H, t, J=7.3 Hz), 3.00 (2H, t, J=7.3 Hz), 2.76 (2H, q, J=7.5 Hz), 2.36 (3H, s), 2.29 (3H, s), 1.31 (3H, t, J=7.5 Hz).

STEP 7. 2-Ethyl-5,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-5,6-dimethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 7.79 (2H, d, J=8.1 Hz), 7.48 (1H, s), 7.29-7.15 (6H, m), 6.86 (1H, s), 6.60 (1H, br.s), 3.57-3.55 (2H, m), 2.91-2.89 (2H, m), 2.70 (2H, q, J=7.5 Hz), 2.39 (3H, s), 2.35 (3H, s), 2.27 (3H, s), 1.25 (3H, t, J=7.5 Hz).

EXAMPLE 95

5,6-DIMETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 2-ethyl-5,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole (Example 94).

¹H-NMR (DMSO-*d*₆) δ 7.60 (2H, d, J=8.1 Hz), 7.39-7.32 (5H, m), 7.13 (2H, d, J=8.1 Hz), 6.86 (1H, s), 3.16 (2H, m), 2.73-2.64 (4H, m), 2.29 (3H, s), 2.27 (3H, s), 2.23 (3H, s), 1.20 (3H, t, J=7.4 Hz); IR (KBr) ν_{max} 1599, 1516, 1468, 1404, 1283, 1236, 1130, 1086 cm⁻¹.

EXAMPLE 965,6-DICHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE5 STEP 1. 2-[4-(4,5-Dichloro-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4,5-trichloronitrobenzene and 4-aminophenylethyl alcohol. MS (EI) m/z 327 (M^+).

STEP 2. 2-[4-(2-Amino-4,5-dichloroanilino)phenyl]ethanol10 The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[4-(4,5-dichloro-2-nitroanilino)phenyl]ethanol (step 1).

$^1\text{H-NMR}$ (CDCl_3) δ 7.16 (1H, s), 7.11 (2H, d, $J=8.0$ Hz), 6.87 (1H, s), 6.74 (2H, d, $J=8.0$ Hz), 5.10 (1H, br.s), 3.90-3.60 (2H, m), 2.79 (2H, t, $J=7.0$ Hz).

STEP 3. 2-[4-(5,6-Dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl15 propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-4,5-dichloroanilino)phenyl]ethanol (step 2) and propionyl chloride.

MS (EI) m/z 390 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 7.84 (1H, s), 7.45 (2H, d, $J=8.1$ Hz), 7.27 (2H, d, $J=8.1$ Hz), 7.16 (1H, s), 4.37 (2H, t, $J=6.8$ Hz), 3.09 (2H, t, $J=6.8$ Hz), 2.77 (2H, q, $J=7.5$ Hz), 2.36 (2H, q, $J=7.5$ Hz), 1.35 (3H, t, $J=7.5$ Hz), 1.16 (3H, t, $J=7.5$ Hz).

STEP 4. 2-[4-(5,6-Dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol

25 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5,6-dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.84 (1H, s), 7.47 (2H, d, J=8.0 Hz), 7.28 (2H, d, J=8.0 Hz), 7.18 (1H, s), 4.10-3.94 (2H, m), 3.01 (2H, t, J=6.4 Hz), 2.77 (2H, q, J=7.5 Hz), 1.34 (3H, t, J=7.5 Hz).

STEP 5. 2-[4-(5,6-Dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide

- 5 The title compound was prepared according to the procedure described in step 5 Example 26 from 2-[4-(5,6-dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

MS (EI) m/z 359 (M⁺); ¹H-NMR (CDCl₃) δ 7.85 (1H, s), 7.46 (2H, d, J=8.1 Hz), 7.28 (2H, d, J=8.1 Hz), 7.17 (1H, s), 3.62 (2H, t, J=7.0 Hz), 3.02 (2H, t, J=7.0 Hz), 2.76 (2H, q, J=7.5 Hz), 1.34 (3H, t, J=7.5 Hz).

STEP 6. 2-[4-(5,6-Dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 2-[4-(5,6-dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

- 15 ¹H-NMR (CDCl₃) δ 7.84 (1H, s), 7.43 (2H, d, J=8.4 Hz), 7.27 (2H, d, J=8.4 Hz), 7.22 (1H, s), 3.14 (2H, t, J=7.2 Hz), 2.97 (2H, t, J=7.2 Hz), 2.76 (2H, q, J=7.6 Hz), 2.10 (2H, br.s), 1.34 (3H, t, J=7.6 Hz).

STEP 7. 5,6-Dichloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl)-1H-benzimidazole

- 20 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(5,6-dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 8.01 (1H, s), 7.70 (2H, d, J=8.3 Hz), 7.46 (2H, d, J=8.3 Hz), 7.36-7.29, (3H, m) 7.24 (2H, d, J=8.3 Hz), 6.81 (1H, br.s), 3.57-3.46 (2H, m), 3.06-2.88 (4H, m), 2.38 (3H, s), 1.43 (3H, t, J=6.9 Hz).

EXAMPLE 97

0997761.101501

2-[4-(5,6-DICHLORO-2-ETHYL-1H-BENZIMIDAZOL-1-
YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in
Example 3 from 2-[4-(5,6-dichloro-2-ethyl-1H-benzimidazol-1-

5 yl)phenyl]ethanol (step 4 of Example 96).

¹H-NMR (CDCl₃) δ 7.92 (2H, d, J=8.4 Hz), 7.85 (1H, s), 7.37 (2H, d, J=8.4 Hz),
7.35 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.16 (1H, s), 4.72 (1H, br.s), 4.38
(2H, t, J=6.8 Hz), 3.03 (2H, t, J=6.8 Hz), 2.75 (2H, q, J=7.5 Hz), 2.44 (3H, s),
1.34 (3H, t, J=7.5 Hz).

10 EXAMPLE 98

5,6-DICHLORO-2-ETHYL-1-(4-{2-[HYDROXY{[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL]AMINO}ETHYL}PH
ENYL)-1H-BENZIMIDAZOLE

15 STEP 1. 1-[4-(2-{(tert-Butoxycarbonyl)[(tert-
butoxycarbonyl)oxy]amino}ethyl)phenyl]-5,6-dichloro-2-ethyl-1H-
benzimidazole

To a stirred mixture of 2-[4-(5,6-dichloro-2-ethyl-1H-benzimidazol-1-
yl)phenyl]ethanol (Example 96, 100 mg, 0.3 mmol), *N,O*-Bis-*tert*-
butoxycarbonylhydroxylamine (Baillie, L.C.; Batsanov, A.; Bearder, J.R.;

20 Whiting, D.A. *J. Chem. Soc. Perkin Trans. 1*, 1998, 20, 3471., 140 mg, 0.6
mmol) and triphenylphosphine (158 mg, 0.6 mmol) in THF (10 mL) was added
diethyl azodicarboxylate (DEAD) (0.1 mL, 0.6 mmol). The mixture was stirred
under nitrogen atmosphere at room temperature for 2.5 h. The solvent was
removed and the residue was purified by flash column chromatography on silica
25 gel eluting with hexane/ethyl acetate (1:1) to afford 174 mg (quant.) of the title
compound as yellow amorphous: ¹H-NMR (CDCl₃) δ 7.84 (1H, s), 7.46 (2H, d,
J=8.4 Hz), 7.25 (2H, d, J=8.4 Hz), 7.16 (1H, s), 3.92 (2H, t, J=6.7 Hz), 3.05 (2H,

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t, J=6.7 Hz), 2.76 (2H, q, J=7.6 Hz), 1.56 (9H, s), 1.46 (9H, s), 1.33 (3H, t, J=7.6 Hz).

STEP 2. *N*-{2-[4-(5,6-Dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl}hydroxylamine

- 5 A mixture of 1-[4-(2-((*tert*-butoxycarbonyl)[(*tert*-butoxycarbonyl)oxy]amino)ethyl)phenyl]-5,6-dichloro-2-ethyl-1*H*-benzimidazole (step 1, 174 mg, 0.3 mmol) and 2*N* hydrochloric acid (3 mL) in ethyl acetate (20 mL) was stirred at room temperature for 1 day. The reaction mixture was poured into water (100 mL), neutralized with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (50 mL), dried (Na₂SO₄), and concentrated to afford 162 mg (quant.) of the title compound as a yellow oil: ¹H-NMR (CDCl₃) δ 10.35 (2H, br.s), 7.89 (1H, s), 7.46-7.50 (2H, m), 7.29 (2H, d, J=6.8 Hz), 7.17 (1H, s), 3.37 (2H, t, J=6.9 Hz), 3.12 (2H, t, J=6.9 Hz), 2.80 (2H, q, J=6.9 Hz), 1.34 (3H, m).
- 10
- 15

STEP 3. 5,6-Dichloro-2-ethyl-1-(4-{2-[hydroxy({[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole

The reaction was carried out according to the procedure described in step 10 of

- 20 Example 1 from *N*-{2-[4-(5,6-dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl}hydroxylamine (step 2).
- MS (ESI) *m/z* 547 (M + H)⁺; ¹H-NMR (CDCl₃) δ: 7.92 (2H, d, J=8.4 Hz), 7.79 (2H, d, J=7.2 Hz), 7.34-7.45 (2H, m), 7.13-7.18 (4H, m), 3.85 (1H, br.s), 3.05 (2H, br.s), 2.66-2.80 (4H, m), 2.38 (3H, s), 1.32 (3H, t, J=7.4 Hz); IR (KBr) ν_{max}
- 25 1654, 1517, 1452, 1164, 1095, 869 cm⁻¹.

EXAMPLE 99

5,6-DICHLORO-2-ETHYL-1-(4-{*cis*-3-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]CYCLOBUTYL}PHENYL)-1*H*-BENZIMIDAZOLE
STEP 1. *trans*-3-Phenylcyclobutyl benzoate

- 5 To a stirred solution of *cis*-3-phenylcyclobutanol (Eckehard, V. D.; *et al. Chem. Ber.*, 1993, 126, 2759., 4.6 g, 30.2 mmol), triphenylphosphine (3.3 g, 59.1 mmol) and benzoic acid (7.6 mg, 62.3 mmol) was added diethyl azodicarboxylate (DEAD) (10.9 g, 62.3 mmol) at room temperature. The resulting mixture was stirred at room temperature for 40 min, then the mixture
- 10 was concentrated. The residue was dissolved in diethyl ether (100 mL) and washed with saturated aqueous sodium bicarbonate (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried (Na₂SO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (10:1) to afford 6.52 g (86%) of the title compound as a
- 15 pale yellow oil: ¹H-NMR (CDCl₃) δ 7.71-7.20 (10H, m), 5.49-5.41 (1H, m), 3.82-3.72 (1H, m), 2.78-2.64 (4H, m).

STEP 2. *trans*-3-Phenylcyclobutanol

- To a solution of *trans*-3-phenylcyclobutyl benzoate (step 1, 6.5 g, 26.0 mmol) in methanol (100 mL) was added 4*N* aqueous LiOH (20 mL, 80 mmol) and the
- 20 resulting mixture was stirred at room temperature for 10 min. The mixture was concentrated. The residue was dissolved in water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (100 mL), dried (Na₂SO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) to afford 3.65 g (93%) of the
- 25 title compound as a colorless oil: ¹H-NMR (CDCl₃) δ 7.34-7.16 (5H, m), 4.60-4.51 (1H, m), 3.69-3.59 (1H, m), 2.55-2.37 (4H, m).

STEP 3. *trans*-3-(4-Nitrophenyl)cyclobutanol

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To a mixture of nitric acid (fuming, 2.3 mL) and acetic anhydride (25 mL) was added dropwise a mixture of *trans*-3-phenylcyclobutyl benzoate (step 2, 3.7 g, 24.6 mmol) and sulfuric acid in acetic anhydride (25 mL) at -23 °C. The resulting mixture was stirred in an ice-bath for 1.5 h. The mixture was poured into ice water (200 mL) and extracted with dichloromethane (2 x 100 mL). The organic layer was washed with water and brine (100 mL), then dried (Na₂SO₄), and concentrated. The oily residue was dissolved in methanol (100 mL), and 4N aqueous LiOH (50 mL) was added. The resulting mixture was stirred at room temperature for 10 min, then concentrated. The residue was dissolved in water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine, dried (Na₂SO₄), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (2:1) to afford 2.7 g (56%) of the title compound as a pale yellow oil: MS (EI) m/z 193 (M⁺); ¹H-NMR (CDCl₃) δ 8.18 (2H, d, J=8.6 Hz), 7.38 (2H, d, J=8.6 Hz), 4.62-4.52 (1H, m), 3.81-3.71 (1H, m), 2.54-2.45 (4H, m).

STEP 4. *trans*-3-(4-Aminophenyl)cyclobutanol

To a stirred solution of *trans*-3-(4-nitrophenyl)cyclobutanol (step 3, 1.0 g, 4.9 mmol) in methanol (20 mL) was added 10% Pd-C (50 mg). The mixture was stirred at room temperature under hydrogen atmosphere for 2.5 h. The palladium catalyst was removed by filtration and washed with methanol (100 mL) and ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure to afford 0.9 g (quant.) of the title compound as pale yellow solids: MS (EI) m/z 163 (M⁺); ¹H-NMR (CDCl₃) δ 7.03 (2H, d, J=8.3 Hz), 6.66 (2H, d, J=8.3 Hz), 4.56-4.47 (1H, m), 3.58-3.48 (3H, m), 2.48-2.31 (2H, m), 1.73 (1H, d, J=5.1 Hz).

STEP 5. *trans*-3-[4-(4,5-Dichloro-2-nitroanilino)phenyl]cyclobutanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4,5-trichloronitrobenzene and *trans*-3-(4-aminophenyl)cyclobutanol (step 4).

¹H-NMR (CDCl₃) δ 9.40 (1H, br.s), 8.27 (1H, s), 7.33 (2H, d, J=8.1 Hz), 7.22 (2H, d, J=8.1 Hz), 7.19 (1H, s), 4.63-4.55 (1H, m), 3.73-3.63 (1H, m), 2.57-2.43 (4H, m).

MS (EI) m/z: 352 (M⁺).

STEP 6. *trans*-3-[4-(2-Amino-4,5-dichloroanilino)phenyl]cyclobutanol

The title compound was prepared according to the procedure described in step 3 of Example 6 from *trans*-3-[4-(4,5-dichloro-2-nitroanilino)phenyl]cyclobutanol (step 5).

¹H-NMR (CDCl₃) δ 7.16 (1H, s), 7.12 (2H, d, J=8.6 Hz), 6.86 (1H, s), 6.75 (2H, d, J=8.6 Hz), 5.08 (1H, br.s), 4.58-4.49 (1H, m), 3.77 (2H, br.s), 3.62-3.52 (1H, m), 2.50-2.34 (4H, m).

STEP 7. *trans*-3-[4-(5,6-Dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]cyclobutyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from *trans*-3-[4-(2-amino-4,5-dichloroanilino)phenyl]cyclobutanol (step 6) and propionyl chloride.

TLC Rf = 0.56 (ethyl acetate/hexane = 1:1).

STEP 8. *trans*-3-[4-(5,6-Dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]cyclobutanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from *trans*-3-[4-(2-amino-4,5-dichloroanilino)phenyl]cyclobutyl propionate (step 7).

MS (EI) m/z : 360 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 7.85 (1H, br.s), 7.45 (2H, d, $J=8.1$ Hz), 7.27 (2H, d, $J=8.1$ Hz), 7.18 (1H, br.s), 4.65-4.55 (1H, m), 3.83-3.73 (1H, m), 2.77 (2H, q, $J=7.5$ Hz), 2.63-2.48 (4H, m), 1.34 (3H, t, $J=7.5$ Hz).

STEP 9. *cis*-3-[4-(5,6-Dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]cyclobutyl azide

To a stirred solution of *trans*-3-[4-(5,6-dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]cyclobutanol (step 8, 572 mg, 1.6 mmol), triphenylphosphine (623 mg, 2.4 mmol) and diphenylphosphoryl azide (DPPA) (655 mg, 2.4 mmol) in THF (8 mL) was added diethyl azodicarboxylate (415 mg, 2.4 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h, then the mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), and concentrated. Purification by flash column chromatography on silica gel eluting with hexane/ethyl acetate (2:1) to afford 506 mg (83%) of the title compound as colorless solids: MS (EI) m/z : 385 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 7.84 (1H, br.s), 7.42 (2H, d, $J=8.3$ Hz), 7.28 (2H, d, $J=8.3$ Hz), 7.17 (1H, br.s), 3.98-3.88 (1H, m), 3.37-3.25 (1H, m), 2.89-2.75 (2H, m), 2.77 (2H, q, $J=7.6$ Hz), 2.34-2.23 (2H, m), 1.34 (3H, t, $J=7.6$ Hz).

STEP 10. *cis*-3-[4-(5,6-Dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]cyclobutylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from *cis*-3-[4-(5,6-dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]cyclobutyl azide (step 9).

MS (EI) m/z 359 (M^+); $^1\text{H-NMR}$ (CDCl_3) δ 7.84 (1H, br.s), 7.41 (2H, d, $J=8.4$ Hz), 7.24 (2H, d, $J=8.4$ Hz), 7.17 (1H, br.s), 3.55-3.43 (1H, m), 3.24-3.12 (1H, m), 2.87-2.73 (4H, m), 1.91-1.80 (2H, m), 1.34 (3H, t, $J=7.5$ Hz).

STEP 11. 5,6-Dichloro-2-ethyl-1-(4-{*cis*-3-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]cyclobutyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step

- 5 10 of Example 1 from *cis*-3-[4-(5,6-dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]cyclobutylamine (step 10).

MS (ESI) *m/z* 557 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.85 (1H, br.s), 7.79 (2H, d, J=8.4 Hz), 7.42 (2H, d, J=8.1 Hz), 7.36 (2H, d, J=8.1 Hz), 7.28 (2H, d, J=8.4 Hz), 7.17 (1H, br.s), 4.35-4.26 (1H, m), 3.35-3.25 (1H, m), 2.93-2.83 (2H, m),
10 2.78 (2H, q, J=7.6 Hz), 2.46 (3H, s), 2.19-2.07 (2H, m), 1.34 (3H, t, J=7.6 Hz).

EXAMPLE 100

5,6-DICHLORO-1-(4-{1,1-DIMETHYL-2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-ETHYL-1*H*-BENZIMIDAZOLE

- 15 STEP 1. 2-[4-(4,5-Dichloro-2-nitroanilino)phenyl]-2-methylpropanenitrile

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4,5-trichloronitroaniline and 2-(4-aminophenyl)-2-methylpropanenitrile (Axton, C.A.; et al. *J.Chem.Soc.Perkin Trans.1*, 1992, 17, 2203).

- 20 ¹H-NMR (CDCl₃) δ 9.38 (1H, br), 8.31 (1H, s), 7.54 (2H, d, J=8.58 Hz), 7.30-7.22 (3H, m), 1.75 (6H, s).

STEP 2. 2-[4-(2-Amino-4,5-dichloroanilino)phenyl]-2-methylpropanenitrile

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[4-(4,5-dichloro-2-nitroanilino)phenyl]-2-

- 25 methylpropanenitrile (step 1).

¹H-NMR (CDCl₃) δ 7.41 (1H, s), 7.30 (2H, d, J=8.4 Hz), 7.09 (1H, s), 6.90 (1H, s), 6.80 (2H, d, J=8.4 Hz), 5.22 (2H, s), 1.62 (6H, s).

STEP 3. 2-[4-(5,6-Dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]-2-methylpropanenitrile

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-4,5-dichloroanilino)phenyl]-2-

methylpropanenitrile (step 2) and propionyl chloride.

¹H-NMR (CDCl₃) δ 7.91 (1H, s), 7.78 (2H, d, J=8.4 Hz), 7.45 (2H, d, J=8.4 Hz), 7.24 (1H, s), 2.83 (2H, q, J=7.5 Hz), 1.89 (6H, s), 1.42 (3H, t, J=7.3 Hz).

STEP 4. 5,6-Dichloro-1-(4-{1,1-dimethyl-2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-2-ethyl-1*H*-benzimidazole

A mixture of 2-[4-(5,6-dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]-2-methylpropanenitrile (step 3, 102 mg, 0.28 mmol), PtO₂ (one portion), chloroform (0.5 mL) in ethanol (15 mL) was stirred under hydrogen atmosphere (4.5 Kg/cm²) at room temperature. After 8 h, the mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was suspended in dichloromethane (10 mL). To the suspension was added *p*-toluenesulfonyl isocyanate (0.3 mL, 1.96 mmol), and triethylamine (0.3 mL, 2.1 mmol) at room temperature. After 0.5 h, the mixture was concentrated. The residue was dissolved in dichloromethane (100 mL) and washed with 10% aqueous citric acid (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried (MgSO₄) and concentrated. The residue was purified by preparative TLC (ethyl acetate/hexane = 2:1) to give 62 mg (37%) of the title compound as white solids: ¹H-NMR (CDCl₃) δ 7.83 (1H, s), 7.67 (2H, d, J=9.3 Hz), 7.55 (2H, d, J=9.3 Hz), 7.38-7.22 (4H, m), 7.18 (1H, s), 3.45 (1H, br), 2.76 (2H, q, J=8.4 Hz), 2.34 (3H, s), 1.37 (6H, s), 1.31 (3H, t, J=8.2 Hz).

EXAMPLE 101

STEP 1. Ethyl [4-(4,5-dichloro-2-nitroanilino)phenyl]acetate

The title compound was prepared according to the procedure described in step 3 of Example 1 from ethyl 2,4,5-trichloronitrobenzene and 4-aminophenylacetate.

¹H-NMR (CDCl₃) δ 9.41 (1H, s), 8.32 (1H, s), 7.37 (2H, d, J=8.4 Hz), 7.28 (1H, s), 7.22 (2H, d, J=8.3 Hz), 4.19 (2H, q, J=7.1 Hz), 3.66 (2H, s), 1.29 (3H, t, J=7.1 Hz).

STEP 2. Ethyl [4-(2-Amino-4,5-dichloroanilino)phenyl]acetate

The title compound was prepared according to the procedure described in step 2 of Example 28 from ethyl [4-(4,5-dichloro-2-nitroanilino)phenyl]acetate (step 1).

¹H-NMR (CDCl₃) δ 7.16 (1H, s), 7.15 (2H, d, J=7.5 Hz), 6.86 (1H, s), 6.72 (2H, d, J=7.1 Hz), 5.12 (1H, br.s), 4.15 (2H, q, J=7.0 Hz), 3.79 (2H, br), 3.54 (2H, s), 1.26 (3H, t, J=7.1 Hz).

STEP 3. Ethyl [4-(5,6-dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]acetate

The title compound was prepared according to the procedure described in step 5 of Example 1 from ethyl [4-(2-amino-4,5-dichloroanilino)phenyl]acetate (step 2) and propionyl chloride.

¹H-NMR (CDCl₃) δ 7.84 (1H, s), 7.52 (2H, d, J=8.2 Hz), 7.30 (2H, d, J=8.4 Hz), 7.19 (1H, s), 4.22 (2H, q, J=7.1 Hz), 3.75 (2H, s), 2.77 (2H, q, J=7.5 Hz), 1.34 (3H, t, J=7.5 Hz), 1.32 (3H, t, J=7.1 Hz).

STEP 4. [4-(5,6-Dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]acetic acid

To a stirred solution of ethyl [4-(5,6-dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]acetate (step 3, 1.30 g, 3.4mmol) in methanol was added 2N aqueous NaOH (3.4 mL) at room temperature. After 1 h, the mixture was concentrated and the residue was diluted in water (200 mL) and the mixture was washed with diethyl ether (100 mL). The aqueous layer was acidified with 2N hydrochloric acid and extracted with ethyl acetate/THF (v/v, 1:1, 300 mL). The organic extract was washed with water (200 mL), brine (200 mL), and dried (MgSO₄). Removal of solvent gave 1.02 g (86%) of the title compound as a white powder.

¹H-NMR (CDCl₃) δ 7.94 (1H, s), 7.56-7.45 (4H, m), 7.26 (1H, s), 3.72 (2H, s), 2.72 (2H, q, J=7.3 Hz), 1.22 (3H, t, J=7.5 Hz).

STEP 5. 2-[4-(5,6-Dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]acetamide

A mixture of [4-(5,6-dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]acetic acid (step 4, 0.81 g, 2.3 mmol) and thionyl chloride (10 mL) was stirred for 0.5 h, and concentrated. To the residue was added ammonium hydroxide (28% NH₃ in water, 50 mL) and the mixture was extracted with ethyl acetate/THF (v/v, 1:1, 200 mL). The extract was washed with brine (2 x 100 mL), dried (MgSO₄), and concentrated. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol (20:1) to give 349 mg (44%) of the title compound as yellow solids: ¹H-NMR (CDCl₃) δ 7.93 (1H, s), 7.58 (1H, br), 7.51 (2H, d, J=8.4 Hz), 7.47 (2H, d, J=8.4 Hz), 7.27 (1H, s), 7.00 (1H, br), 3.51 (2H, s), 2.71 (2H, q, J=7.5 Hz), 1.21 (3H, t, J=7.5 Hz).

STEP 6. 2-[4-(5,6-Dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]-*N*-(4-methylphenyl)sulfonyl]amino}carbonyl]acetamide

A mixture of 2-[4-(5,6-dichloro-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]acetamide (step 5, 105 mg, 0.30 mmol), *p*-toluenesulfonyl isocyanate (0.07 mL, 0.45 mmol), toluene (10 mL) and THF (5 mL) was heated at reflux temperature. After 6 h, an additional 0.1 mL of *p*-toluenesulfonyl isocyanate was added and the mixture was heated for 3 h. The mixture was cooled and left at room temperature for 2 days. The mixture was concentrated and the residue was purified by preparative TLC (ethyl acetate) to afford 150 mg (92%) of the title compound as colorless amorphous solids: ¹H-NMR (CDCl₃) δ 9.78 (1H, s), 7.95 (2H, d, J=8.3 Hz), 7.84 (1H, s), 7.54 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.0 Hz), 7.32 (2H, d, J=8.4 Hz), 7.18 (1H, s), 3.78 (2H, s), 2.77 (2H, q, J=7.5 Hz), 2.41 (3H, s), 1.35 (3H, t, J=7.5 Hz).

EXAMPLE 102

5,6-DICHLORO-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2-[4-(5,6-Dichloro-1H-benzimidazol-1-yl)phenyl]ethyl formate

- 5 A mixture of 2-[(4,5-dichloro-2-anilino)phenyl]ethanol (450 mg, 1.42 mmol) and formic acid (7 mL) was stirred at reflux for 4 h. After cooling, the mixture was made basic with 2N aqueous NaOH and extracted with ethyl acetate (50 mL). The extracts was dried (MgSO₄) to afford 480 mg (quant.) of the title compound as a brown oil: ¹H-NMR (CDCl₃) δ 8.10 (1H, s), 8.08 (1H, s), 7.95 (1H, s), 7.61 (1H, s), 7.49-7.41 (4H, m), 4.47 (2H, t, J=6.8 Hz), 3.10 (2H, t, J=6.8 Hz).

STEP 2. 2-[4-(5,6-Dichloro-1H-benzimidazol-1-yl)phenyl]ethanol

- The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5,6-dichloro-1H-benzimidazol-1-yl)phenyl]ethyl formate (step 1).
- 15 ¹H-NMR (CDCl₃) δ 8.08 (1H, s), 7.96 (1H, s), 7.61 (1H, s), 7.49-7.40 (4H, m), 3.97 (2H, q, J=6.4 Hz), 2.99 (2H, t, J=6.4 Hz).

STEP 3. 2-[4-(5,6-Dichloro-1H-benzimidazol-1-yl)phenyl]ethyl azide

- The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(5,6-dichloro-1H-benzimidazol-1-yl)phenyl]ethanol (step 2).
- MS (EI) m/z 332 (M⁺).

STEP 4. 2-[4-(5,6-Dichloro-1H-benzimidazol-1-yl)phenyl]ethylamine

- The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(5,6-dichloro-1H-benzimidazol-1-yl)phenyl]ethyl azide (step 3).

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¹H-NMR (CDCl₃) δ 8.09 (1H, s), 7.96 (1H, s), 7.62 (1H, s), 7.45-7.38 (4H, m), 3.06 (2H, m), 2.87 (2H, t, J=6.6 Hz).

STEP 5. 5,6-Dichloro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)aminoethyl}phenyl)-1H-benzimidazole

- 5 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(5,6-dichloro-1H-benzimidazol-1-yl)phenyl]ethylamine (step 3).

¹H-NMR (CDCl₃) δ 8.11 (1H, s), 7.96 (1H, s), 7.72 (2H, d, J=8.4 Hz), 7.58 (1H, s), 7.38 (4H, s), 7.28 (2H, d, J=8.4 Hz), 6.72 (1H, m), 3.56 (2H, q, J=6.9 Hz), 2.92 (2H, t, J=6.9 Hz), 2.38 (3H, s).

EXAMPLE 103

5,6-DICHLORO-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINOETHYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

- 15 The title compound was prepared according to the procedure described in Example 2 from 5,6-dichloro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)aminoethyl}phenyl)-1H-benzimidazole (Example 102).

¹H-NMR (DMSO-d₆) δ 8.55 (1H, s), 7.97 (1H, s), 7.71 (1H, s), 7.50-7.44 (4H, m), 7.29 (2H, d, J=8.4 Hz), 7.01 (2H, d, J=8.4 Hz), 3.02 (2H, m), 2.61 (2H, m), 2.16 (3H, s); IR (KBr) ν_{max} 1601, 1516, 1487, 1450, 1128, 1084 cm⁻¹.

EXAMPLE 104

6-CHLORO-5-TRIFLUOROMETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINOETHYL}PHENYL)-1H-BENZIMIDAZOLE

- 25)-1H-BENZIMIDAZOLE

STEP 1. 2-[(5-Chloro-4-trifluoromethyl-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4-dichloro-5-trifluoromethylnitrobenzene and 4-aminophenylethyl alcohol.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ 9.69 (1H, br.s), 8.58 (1H, s), 7.37 (2H, d, $J=8.4$ Hz), 7.23 (2H, d, $J=8.4$ Hz), 7.19 (1H, s), 3.93 (2H, t, $J=6.4$ Hz), 2.94 (2H, t, $J=6.4$ Hz).

STEP 2. 2-[(2-Amino-5-chloro-4-trifluoromethylanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[(5-chloro-4-trifluoromethyl-2-nitroanilino)phenyl]ethanol (step 1).

- 10 $^1\text{H-NMR}$ (CDCl_3) δ 7.17-7.15 (3H, m), 7.05 (1H, s), 6.92-6.88 (2H, m), 5.48 (1H, br.s), 3.85 (2H, t, $J=6.6$ Hz), 2.83 (2H, t, $J=6.6$ Hz).

STEP 3. 2-[4-(6-Chloro-2-ethyl-5-trifluoromethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

- 15 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-5-chloro-4-trifluoromethylanilino)phenyl]ethanol (step 2) and propionyl chloride.
MS (EI) 424 (M^+).

STEP 4. 2-[4-(6-Chloro-2-ethyl-5-trifluoromethyl-1H-benzimidazol-1-yl)phenyl]ethanol

- 20 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-chloro-2-ethyl-5-trifluoromethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).
 $^1\text{H-NMR}$ (CDCl_3) δ 8.11 (1H, s), 7.50 (2H, d, $J=8.3$ Hz), 7.29 (2H, d, $J=8.3$ Hz),
25 7.21 (1H, s), 4.03-3.98 (2H, m), 3.02 (2H, t, $J=6.4$ Hz), 2.79 (2H, q, $J=7.5$ Hz), 1.36 (3H, t, $J=7.5$ Hz).

STEP 5 2-[4-(6-Chloro-2-ethyl-5-trifluoromethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(6-Chloro-2-ethyl-5-trifluoromethyl-1*H*-benzimidazol-

1-yl)phenyl]ethanol
(step 4).

¹H-NMR (CDCl₃) δ 8.11 (1H, s), 7.49 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 7.20 (1H, s), 3.63 (2H, t, J=6.9 Hz), 3.03 (2H, t, J=6.9 Hz), 2.79 (2H, q, J=7.4 Hz), 1.36 (3H, t, J=7.4 Hz).

STEP 6. 2-[4-(6-Chloro-2-ethyl-5-trifluoromethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(6-chloro-2-ethyl-5-trifluoromethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 8.11 (1H, s), 7.45 (2H, d, J=8.3 Hz), 7.29-7.26 (2H, m), 7.23 (1H, s), 3.11 (2H, t, J=7.0 Hz), 2.92 (2H, t, J=7.0 Hz), 2.79 (2H, q, J=7.5 Hz), 1.36 (3H, t, J=7.5 Hz).

STEP 7 2-Ethyl-6-chloro-5-trifluoromethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(6-chloro-2-ethyl-5-trifluoromethyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 8.09 (1H, s), 7.74 (2H, d, J=8.4 Hz), 7.42 (2H, d, J=8.2 Hz), 7.30-7.26 (4H, m), 7.18 (1H, s), 6.76 (1H, m), 3.59 (2H, q, J=7.0 Hz), 2.96 (2H, t, J=7.0 Hz), 2.79 (2H, q, J=7.6 Hz), 1.34 (3H, t, J=7.6 Hz).

EXAMPLE 105

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6-CHLORO-5-TRIFLUOROMETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in

- 5 Example 2 from 2-ethyl-6-chloro-5-trifluoromethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino}ethyl}phenyl)-1H-benzimidazole (Example 104).

¹H-NMR (DMSO-d₆) δ 8.15 (1H, s), 7.59 (2H, d, J=8.4 Hz), 7.46-7.39 (4H, m), 7.33 (1H, s), 7.12 (2H, d, J=8.4 Hz), 3.15 (2H, m), 2.78-2.71 (4H, m), 1.24 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 1601, 1518, 1431, 1398, 1348, 1306, 1128, 1084 cm⁻¹.

EXAMPLE 106

4-(6-CHLORO-2-ETHYL-5-TRIFLUOROMETHYL-1H-BENZIMIDAZOL-1-YL)PHENETHYL-(4-METHYLPHENYL)SULFONYLCARBAMATE

- 15 The title compound was prepared according to the procedure described in Example 3 from 2-[4-(6-chloro-2-ethyl-5-trifluoromethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4 of Example 104).

mp 170-173 °C; ¹H-NMR (CDCl₃) δ 8.12 (1H, s), 7.94-7.91 (2H, m), 7.41-7.24 (6H, m), 7.19 (1H, s), 4.39 (2H, t, J=6.8 Hz), 3.04 (2H, t, J=6.8 Hz), 2.78 (2H, q, J=7.6 Hz), 2.44 (3H, s), 1.35 (3H, t, J=7.6 Hz); IR (KBr) ν_{max} 1746, 1518, 1342, 1232, 1159, 1132, 1086 cm⁻¹.

EXAMPLE 107

4-(6-CHLORO-2-ETHYL-5-TRIFLUOROMETHYL-1H-BENZIMIDAZOL-1-YL)PHENETHYL-(4-METHYLPHENYL)SULFONYLCARBAMATE, SODIUM SALT

- 25 The title compound was prepared according to the procedure described in Example 2 from 4-(6-chloro-2-ethyl-5-trifluoromethyl-1H-benzimidazol-1-yl)phenethyl-(4-methylphenyl)sulfonylcarbamate (Example 106).

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¹H-NMR (DMSO-d₆) δ 8.15 (1H, s), 7.59 (2H, d, J=8.1 Hz), 7.47 (4H, s), 7.34 (1H, s), 7.15 (2H, d, J=8.1 Hz), 3.96 (2H, t, J=6.6 Hz), 2.86 (2H, t, J=6.6 Hz), 2.75 (2H, q, J=7.4 Hz), 2.28 (3H, s), 1.24 (3H, t, J=7.4 Hz).

EXAMPLE 108

5 5-CHLORO-6-METHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2-[(4-Chloro-5-methyl-2-nitroanilino)phenyl]ethanol

10 The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,5-dichloro-4-methylnitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.40 (1H, s), 8.20 (1H, s), 7.31 (2H, d, J=8.4 Hz), 7.21 (2H, d, J=8.4 Hz), 7.05 (1H, s), 3.93-3.91 (2H, m), 2.91 (2H, t, J=6.4 Hz), 2.29 (3H, s)

15 STEP 2. 2-[(2-Amino-4-chloro-5-methylanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[(4-chloro-5-methyl-2-nitroanilino)phenyl]ethanol (step 1).

20 ¹H-NMR (CDCl₃) δ 7.06 (2H, d, J=8.6 Hz), 6.93 (1H, s), 6.79 (1H, s), 6.67 (2H, d, J=8.6 Hz), 3.80 (2H, d, J=6.4 Hz), 2.77 (2H, t, J=6.4 Hz), 2.21 (3H, s).

STEP 3. 2-[4-(5-Chloro-2-ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

25 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[(2-amino-4-chloro-5-methylanilino)phenyl]ethanol (step 2) and propionyl chloride.

MS (EI) m/z 370 (M⁺).

STEP 4. 2-[4-(5-Chloro-2-ethyl-6-methyl-1H-benzimidazol-1-yl)phenyl]ethanol

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The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5-chloro-2-ethyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.74 (1H, s), 7.47 (2H, d, J=8.3 Hz), 7.27 (2H, d, J=8.3 Hz), 6.93 (1H, s), 4.00 (2H, t, J=6.6 Hz), 3.02 (2H, t, J=6.6 Hz), 2.76 (2H, q, J=7.5 Hz), 2.39 (3H, s), 1.32 (3H, t, J=7.5 Hz).

STEP 5. 2-[4-(5-Chloro-2-ethyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-[4-(5-chloro-2-ethyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 7.75 (1H, s), 7.45 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 7.27 (1H, s), 3.62 (2H, t, J=7.0 Hz), 3.02 (2H, t, J=7.0 Hz), 2.76 (2H, q, J=7.5 Hz), 2.40 (3H, s), 1.33 (3H, t, J=7.5 Hz).

STEP 6. 2-[4-(5-Chloro-2-ethyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(5-chloro-2-ethyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl azide (step 5).

¹H-NMR (CDCl₃) δ 7.75 (1H, s), 7.42 (2H, d, J=8.3 Hz), 7.27 (2H, d, J=8.3 Hz), 6.93 (1H, s), 3.10 (2H, t, J=7.0 Hz), 2.90 (2H, t, J=7.0 Hz), 2.76 (2H, q, J=7.5 Hz), 2.40 (3H, s), 1.33 (3H, t, J=7.5 Hz).

STEP 7. 2-Ethyl-5-chloro-6-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(5-chloro-2-ethyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethylamine (step 6).

¹H-NMR (CDCl₃) δ 7.75-7.72 (3H, m), 7.38-7.23 (6H, m), 6.91 (1H, s), 6.73-6.69 (1H, m), 3.62-3.55 (2H, m), 2.94 (2H, t, J=6.8 Hz), 2.75 (2H, q, J=7.6 Hz), 2.40 (3H, s), 2.37 (3H, s), 1.30 (3H, t, J=7.6 Hz).

EXAMPLE 109

5 5-CHLORO-6-METHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in

10 methylphenyl)sulfonyl]amino]carbonyl)amino]ethyl}phenyl)-1H-benzimidazole (Example 108).

¹H-NMR (DMSO-d₆) δ 7.68 (1H, s), 7.60 (2H, d, J=8.1 Hz), 7.41-7.35 (4H, m), 7.13 (2H, d, J=8.1 Hz), 7.05 (1H, s), 3.17-3.15 (2H, m), 2.75-2.65 (4H, m), 2.34 (3H, s), 2.27 (3H, s), 1.20 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 1599, 1516, 1456, 1402, 1128, 1084, 1001 cm⁻¹.

EXAMPLE 110

6-CHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-5-[(METHYLSULFONYL)AMINO]-1H-BENZIMIDAZOLE

20 STEP 1. 2-[4-(5-Chloro-2,4-dinitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4-dichloro-1,5-dinitrobenzene and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.81 (1H, br.s), 9.07 (1H, s), 7.40 (2H, d, J=8.3 Hz), 7.25 (2H, d, J=8.3 Hz), 7.17 (1H, s), 3.95 (2H, t, J=6.6 Hz), 2.95 (2H, t, J=6.6 Hz).

STEP 2. 2-[4-(2-Amino-5-chloro-4-nitroanilino)phenyl]ethanol

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The title compound was prepared according to the procedure described in step 2 of Example 40 from 2-[4-(5-chloro-2,4-dinitroanilino)phenyl]ethanol (step 1).

¹H-NMR (CDCl₃) δ 7.54 (1H, s), 7.24 (2H, d, J=8.6 Hz), 7.11 (1H, s), 7.03 (2H, d, J=8.6 Hz), 5.76 (1H, br.s), 3.89 (2H, t, J=6.4 Hz), 3.65 (2H, br.s), 2.87 (2H, t, J=6.4 Hz), 1.28 (1H, s).

STEP 3. 2-[4-(6-Chloro-2-ethyl-5-nitro-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-(2-amino-5-chloro-4-nitroanilino)phenyl]ethanol (step 2) and propionyl chloride.

TLC Rf = 0.8 (hexane/ethyl acetate = 1:2).

STEP 4. 2-[4-(6-Chloro-2-ethyl-5-nitro-1H-benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-amino-5-chloro-4-nitroanilino)phenyl]ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 8.34 (1H, s), 7.50 (2H, d, J=8.0 Hz), 7.28 (2H, d, J=8.0 Hz), 7.19 (1H, s), 4.00 (2H, t, J=6.3 Hz), 3.02 (2H, t, J=6.3 Hz), 2.79 (2H, q, J=7.6 Hz), 1.62 (1H, s), 1.36 (3H, t, J=7.6 Hz).

STEP 5. 6-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-5-nitro-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(6-chloro-2-ethyl-5-nitro-1H-benzimidazol-1-yl)phenyl]ethanol (step 4).

¹H-NMR (CDCl₃) δ 8.34 (1H, s), 7.50 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 7.19 (1H, s), 3.84 (2H, t, J=7.0 Hz), 3.22 (2H, t, J=7.0 Hz), 2.80 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz).

STEP 6. 6-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-ylamine

The title compound was prepared according to the procedure described in step 4 of Example 89 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-5-nitro-1*H*-benzimidazole (step 5).

¹H-NMR (CDCl₃) δ 7.43 (2H, d, J=8.6 Hz), 7.29 (2H, d, J=8.6 Hz), 7.16 (1H, s), 7.02 (1H, s), 3.96 (2H, br.s), 3.81 (2H, t, J=7.1 Hz), 3.19 (2H, t, J=7.1 Hz), 2.74 (2H, q, J=7.5 Hz), 1.33 (3H, t, J=7.5 Hz).

STEP 7. *N*-{6-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide

The title compound was prepared according to the procedure described in step 5 of Example 40 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-ylamine (step 6).

¹H-NMR (CDCl₃) δ 7.70 (1H, s), 7.55 (2H, d, J=7.9 Hz), 7.50 (2H, d, J=7.9 Hz), 7.13 (1H, s), 3.95 (2H, t, J=7.0 Hz), 3.16 (2H, t, J=7.0 Hz), 2.97 (3H, s), 2.71 (2H, q, J=7.6 Hz), 1.21 (3H, t, J=7.6 Hz).

STEP 8. *N*-{1-[4-(2-Azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide

The title compound was prepared according to the procedure described in step 8 of Example 1 from *N*-{6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide (step 7).

¹H-NMR (CDCl₃) δ 7.47 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.16 (1H, s), 6.78 (1H, s), 3.63 (2H, t, J=6.9 Hz), 2.98-3.05 (5H, m), 2.77 (2H, q, J=7.4 Hz), 1.35 (3H, t, J=7.4 Hz).

STEP 9. *N*-{1-[4-(2-Aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide

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The title compound was prepared according to the procedure described in step 7 of Example 37 from *N*-{1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide (step 8).

¹H-NMR (CDCl₃) δ 8.03 (1H, s), 7.43 (2H, d, J=8.4 Hz), 7.26 (2H, d, J=8.4 Hz), 7.17 (1H, s), 3.33 (2H, br.s), 3.08 (2H, t, J=7.0 Hz), 2.96 (3H, s), 2.88 (2H, t, J=7.0 Hz), 2.77 (2H, q, J=7.6 Hz), 1.35 (3H, t, J=7.6 Hz).

STEP 10. 6-Chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-5-[(methylsulfonyl)amino]-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from *N*-{1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}methanesulfonamide (step 9).

mp 101-123 °C; MS (ESI) *m/z* 590 (M + H)⁺; ¹H-NMR (CDCl₃) δ 8.04 (1H, s), 7.73 (2H, d, J=8.2 Hz), 7.42 (2H, d, J=8.2 Hz), 7.25-7.33 (4H, m), 7.16 (1H, s), 6.68 (1H, br.s), 3.58 (2H, t, J=7.2 Hz), 2.93-2.98 (5H, m), 2.77 (2H, q, J=7.5 Hz), 2.45 (3H, s), 1.35 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 1654, 1517, 1467, 1336, 1151, 1089, 972 cm⁻¹.

EXAMPLE 111

6-CHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE-5-CARBOXAMIDE

STEP 1. 2-Chloro-4-[4-(2-hydroxyethyl)anilino]-5-nitrobenzonitrile

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4-dichloro-5-nitrobenzonitrile (Grivsky, E.M.; Hitchings, G.H. *Ind. Chim. Belge.*, 1974, 39. 490.) and 4-aminophenylethyl alcohol.

¹H-NMR (CDCl₃) δ 9.81 (1H, br.s), 8.56 (1H, s), 7.39 (2H, d, J=8.3 Hz), 7.23 (2H, d, J=8.3 Hz), 7.15 (1H, s), 3.93 (2H, t, J=6.2 Hz), 2.94 (2H, t, J=6.2 Hz), 1.62 (1H, br.s).

STEP 2. 5-amino-2-chloro-4-[4-(2-hydroxyethyl)anilino]benzonitrile

- 5 The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-chloro-4-[4-(2-hydroxyethyl)anilino]-5-nitrobenzonitrile (step 1).

¹H-NMR (CDCl₃) δ 7.23 (4H, d, J=8.3 Hz), 6.99-7.33 (2H, m), 3.88 (2H, t, J=6.1 Hz), 3.56 (1H, br.s), 2.87 (2H, t, J=6.1 Hz).

- 10 STEP 3. 2-[4-(6-Chloro-5-cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 5-amino-2-chloro-4-[4-(2-hydroxyethyl)anilino]benzonitrile (step 2) and propionyl chloride.

- 15 TLC R_f = 0.5 (hexane/ethyl acetate = 1:2).

STEP 4. 6-Chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazole-5-carbonitrile

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-chloro-5-cyano-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).

- 20 ¹H-NMR (CDCl₃) δ 8.04 (1H, s), 7.52 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.19 (1H, s), 4.02 (2H, t, J=6.5 Hz), 3.03 (2H, t, J=6.5 Hz), 2.80 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

STEP 5. 6-Chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazole-5-carboxamide

- 25 To a mixture of 6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazole-5-carbonitrile (step 4, 2.4 g, 7.4 mmol), DMSO (0.7 mL, 8.8

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mmol) and methanol (100 mL) was added 30% aqueous hydrogen peroxide (1.3 mL, 11 mmol) and 0.2 M aqueous NaOH (0.7 mL, 0.14 mmol). The mixture was stirred at 50 °C for 2 h. The solvent was removed and the resulting precipitates were collected by filtration. The precipitates were washed with

water and dried under reduced pressure to give 1.9 g (76%) of the title compound as pale pink solids: $^1\text{H-NMR}$ (DMSO- d_6) δ 7.69 (1H, br.s), 7.61 (1H, s), 7.33-7.40 (4H, m), 6.95 (1H, s), 4.64 (1H, br.s), 3.59 (2H, t, $J=6.4$ Hz), 2.74 (2H, t, $J=6.4$ Hz), 2.62 (2H, q, $J=7.4$ Hz), 1.11 (3H, t, $J=7.4$ Hz).

STEP 6. 6-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 7 of Example 1 from 6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazole-5-carboxamide (step 5).

$^1\text{H-NMR}$ (DMSO- d_6) δ 7.71 (1H, br.s), 7.62 (1H, s), 7.36-7.47 (5H, m), 6.95 (1H, s), 3.85 (2H, t, $J=7.1$ Hz), 3.06 (2H, t, $J=7.1$ Hz), 2.63 (2H, q, $J=7.6$ Hz), 1.11 (3H, t, $J=7.6$ Hz).

STEP 7. 1-[4-(2-Azidoethyl)phenyl]-6-chloro-2-ethyl-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-5-carboxamide (step 6).

$^1\text{H-NMR}$ (DMSO- d_6) δ 7.80 (1H, br.s), 7.71 (1H, s), 7.46-7.57 (5H, m), 7.04 (1H, s), 3.65 (2H, t, $J=6.9$ Hz), 2.98 (2H, t, $J=6.9$ Hz), 2.72 (2H, q, $J=7.5$ Hz), 1.21 (3H, t, $J=7.5$ Hz).

STEP 8. 1-[4-(2-Aminoethyl)phenyl]-6-chloro-2-ethyl-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazole-5-carboxamide (step 7).

¹H-NMR (CDCl₃) δ 7.80 (1H, s), 7.71 (1H, s), 7.39-7.50 (5H, m), 7.08 (1H, s), 2.49-2.89 (6H, m), 1.21 (3H, t, J=7.4 Hz).

STEP 9. 6-Chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazole-5-carboxamide (step 8).

mp 152-163 °C; MS (ESI) m/z 540 (M + H)⁺; ¹H-NMR (DMSO-d₆) δ 7.81 (1H, br.s), 7.72-7.75 (3H, m), 7.51 (1H, br.s), 7.33-7.44 (6H, m), 7.06 (1H, s), 3.26 (2H, br.s), 2.68-2.80 (4H, m), 2.34 (3H, s), 1.23 (3H, t, J=7.5 Hz); IR (KBr) ν_{max} 3395, 1664, 1519, 1396, 1161, 1089, 991 cm⁻¹.

EXAMPLE 112

6-CHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE-5-CARBOXYLIC ACID

A mixture of 6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide (Example 111, 140 mg, 0.26 mmol) and KOH (63 mg, 0.8 mmol) in methanol (10 mL) was stirred at 100 °C for 1 day. The mixture was poured into water, acidified with 2N hydrochloric acid, and extracted with ethyl acetate (50 mL). The organic layer was washed with brine (30 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane/methanol

(10:1) to afford 36 mg (25%) of the title compound as white solids: mp 145-150 °C; MS (ESI) m/z 541 ($M + H$)⁺; ¹H-NMR (DMSO- d_6) δ 8.10 (1H, s), 7.76 (2H, d, $J=7.9$ Hz), 7.36-7.47 (6H, m), 7.10 (1H, s), 3.28 (2H, m), 2.69-2.81 (4H, m), 2.34 (3H, s), 1.24 (3H, t, $J=7.5$ Hz); IR (KBr) ν_{max} : 3450, 1701, 1517, 1340, 1163, 1091, 900 cm^{-1} .

EXAMPLE 113

N-[6-CHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL]-1*H*-BENZIMIDAZOL-5-YL]ACETAMIDE

STEP 1. *N*-[6-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl]acetamide

To a solution of 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-ylamine (step 6 of Example 110, 100 mg, 0.3 mmol) in pyridine (7 mL) was added dropwise acetyl chloride (0.03 mL, 0.33 mmol) under nitrogen

atmosphere at 0 °C, and the reaction mixture was stirred at room temperature for 1.5 h. The mixture was poured into water (20 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with 2N aqueous NaOH (30 mL), brine (30 mL), then dried (Na_2SO_4). After removal of solvent, the crude product was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:3) to afford 110 mg (98%) of the title compound as white solids: ¹H-NMR ($CDCl_3$) δ : 8.66 (1H, s), 7.56 (1H, br.s), 7.45 (2H, d, $J=8.2$ Hz), 7.29 (2H, d, $J=8.2$ Hz), 7.12 (1H, s), 3.82 (2H, t, $J=7.1$ Hz), 3.19 (2H, t, $J=7.1$ Hz), 2.77 (2H, q, $J=7.6$ Hz), 2.26 (3H, s), 1.34 (3H, t, $J=7.6$ Hz).

STEP 2. *N*-[1-[4-(2-Azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl]acetamide

The title compound was prepared according to the procedure described in step 8 of Example 1 from *N*-{6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}acetamide (step 1).

¹H-NMR (DMSO-*d*₆) δ 8.66 (1H, s), 7.55 (1H, br.s), 7.45 (2H, d, *J*=8.1 Hz), 7.30 (2H, d, *J*=8.1 Hz), 7.11 (1H, s), 3.62 (2H, t, *J*=7.1 Hz), 3.02 (2H, t, *J*=7.1 Hz), 2.76 (2H, q, *J*=7.6 Hz), 2.26 (3H, s), 1.34 (3H, t, *J*=7.6 Hz).

STEP 3. *N*-{1-[4-(2-Aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}acetamide

The title compound was prepared according to the procedure described in step 7 of Example 37 from *N*-{1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}acetamide (step 2).

¹H-NMR (CDCl₃) δ 8.66 (1H, s), 7.55 (1H, br.s), 7.42 (2H, d, *J*=6.6 Hz), 7.27-7.29 (2H, m), 7.12 (1H, s), 3.08 (2H, t, *J*=6.9 Hz), 2.88 (2H, t, *J*=6.9 Hz), 2.75 (2H, q, *J*=7.4 Hz), 2.26 (3H, s), 1.34 (3H, t, *J*=7.4 Hz).

STEP 4. *N*-[6-Chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl]phenyl]-1*H*-benzimidazol-5-yl]acetamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from *N*-{1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}acetamide (step 3).

mp 125-133 °C; MS (ESI) *m/z* 554 (*M* + *H*)⁺; ¹H-NMR (CDCl₃) δ 8.64 (1H, s), 7.74 (2H, d, *J*=8.4 Hz), 7.55 (1H, br.s), 7.25-7.39 (1H, s), 7.08 (1H, s), 3.53-3.61 (2H, m), 2.94 (2H, t, *J*=7.1 Hz), 2.75 (2H, q, *J*=7.4 Hz), 2.41 (3H, s), 2.27 (3H, s), 1.32 (3H, t, *J*=7.4 Hz); IR (KBr) *v*_{max} 3390, 1676, 1517, 1240, 1161, 1089, 1018, 972 cm⁻¹.

EXAMPLE 114

6-ETHYL-5-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-5H-[1,3]DIOXOLO[4,5-f]BENZIMIDAZOLE
STEP 1. 2-{4-[(6-Nitro-1,3-benzodioxol-5-yl)amino]phenyl}ethanol

- 5 The title compound was prepared according to the procedure described in step 1 of Example 45 from 5-amino-6-nitro-1,3-benzodioxol and 4-bromophenylethyl alcohol.

¹H-NMR (CDCl₃) δ:10.07 (1H, br.s), 7.62 (1H, s), 7.29 (2H, d, J=8.5 Hz), 7.20 (2H, d, J=8.5 Hz), 6.58 (1H, s), 5.98 (2H, s), 3.90 (2H, t, J=6.6 Hz), 2.90 (2H, t, J=6.6 Hz).

- 10 STEP 2. 2-{4-[(6-Amino-1,3-benzodioxol-5-yl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[(6-nitro-1,3-benzodioxol-5-yl)amino]phenyl}ethanol (step 1).

- 15 ¹H-NMR (CDCl₃) δ 7.26 (1H, s), 7.04 (2H, d, J=8.2 Hz), 6.60 (2H, d, J=8.2 Hz), 6.39 (1H, s), 5.87 (2H, s), 4.96 (1H, br.s), 3.80 (2H, t, J=6.4 Hz), 3.64 (2H, br.s), 2.76 (2H, t, J=6.4 Hz).

STEP 3. 2-[4-(6-Ethyl-5H-[1,3]dioxolo[4,5-f]benzimidazol-5-yl)phenyl]ethyl propionate

- 20 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(6-amino-1,3-benzodioxol-5-yl)amino]phenyl}ethanol (step 2) and propionyl alcohol.

TLC Rf = 0.5 (hexane/ethyl acetate = 1:2).

STEP 4. 2-[4-(6-Ethyl-5H-[1,3]dioxolo[4,5-f]benzimidazol-5-yl)phenyl]ethanol

- 25 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[(6-amino-1,3-benzodioxol-5-yl)amino]phenyl}ethyl propionate (step 3).

¹H-NMR (CDCl₃) δ 7.43 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 7.19 (1H, s), 6.53 (1H, s), 5.94 (2H, s), 3.98 (2H, t, J=6.4 Hz), 2.99 (2H, t, J=6.4 Hz), 2.73 (2H, q, J=7.4 Hz), 1.31 (3H, t, J=7.4 Hz).

STEP 5. 5-[4-(2-Chloroethyl)phenyl]-6-ethyl-5H-[1,3]dioxolo[4,5-

5 f]benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(6-ethyl-5H-[1,3]dioxolo[4,5-f]benzimidazol-5-yl)phenyl]ethanol (step 4).

10 ¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.1 Hz), 7.28 (2H, d, J=8.1 Hz), 7.19 (1H, s), 6.54 (1H, s), 5.94 (2H, s), 3.81 (2H, t, J=7.1 Hz), 3.19 (2H, t, J=7.1 Hz), 2.72 (2H, q, J=7.6 Hz), 1.31 (3H, t, J=7.6 Hz).

STEP 6. 2-[4-(6-Ethyl-5H-[1,3]dioxolo[4,5-f]benzimidazol-5-yl)phenyl]ethyl azide

15 The title compound was prepared according to the procedure described in step 8 of Example 1 from 5-[4-(2-chloroethyl)phenyl]-6-ethyl-5H-[1,3]dioxolo[4,5-f]benzimidazole (step 5).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 7.19 (1H, s), 6.53 (1H, s), 5.93 (2H, s), 3.60 (2H, t, J=7.1 Hz), 3.00 (2H, t, J=7.1 Hz), 2.73 (2H, q, J=7.6 Hz), 1.31 (3H, t, J=7.6 Hz).

20 STEP 7. 2-[4-(6-Ethyl-5H-[1,3]dioxolo[4,5-f]benzimidazol-5-yl)phenyl]ethylamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(6-ethyl-5H-[1,3]dioxolo[4,5-f]benzimidazol-5-yl)phenyl]ethyl azide (step 6).

25 ¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.2 Hz), 7.22-7.28 (2H, m), 7.19 (1H, s), 6.54 (1H, s), 5.93 (2H, s), 3.05 (2H, t, J=6.8 Hz), 2.86 (2H, t, J=6.8 Hz), 2.73 (2H, q, J=7.6 Hz), 1.31 (3H, t, J=7.6 Hz).

STEP 8. 6-Ethyl-5-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-5H-[1,3]dioxolo[4,5-f]benzimidazole

The title compound was prepared according to the procedure described in step

- 5 10 of Example 1 from 2-[4-(6-ethyl-5H-[1,3]dioxolo[4,5-f]benzimidazol-5-yl)phenyl]ethylamine (step 7).

MS (ESI) m/z 507 (M + H)⁺; ¹H-NMR (DMSO-d₆) δ 7.75 (2H, d, J=8.1 Hz), 7.35-7.37 (6H, m), 7.16 (1H, s), 6.55 (1H, s), 5.97 (2H, s), 2.76 (2H, t, J=6.9 Hz), 2.65 (2H, q, J=7.6 Hz), 2.50 (2H, br.s), 2.34 (3H, s), 1.18 (3H, t, J=7.6 Hz).

10 EXAMPLE 115

6-ETHYL-5-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-5H-[1,3]DIOXOLO[4,5-f]BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in

- 15 Example 2 from 6-ethyl-5-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-5H-[1,3]dioxolo[4,5-f]benzimidazole (Example 114).

mp 140-155 °C; IR (KBr) ν_{\max} 3384, 2873, 1600, 1519, 1460, 1155, 1128, 1085, 1037, 945, 813 cm⁻¹.

20 EXAMPLE 116

2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-6,7-DIHYDRO-1H-[1,4]DIOXINO[2,3-f]BENZIMIDAZOLE
STEP 1. 7-Nitro-2,3-dihydro-1,4-benzodioxin-6-amine

- 25 To a mixture of 6,7-dinitro-2,3-dihydrobenzo[1,4]dioxin (Takakis, I.M.; Hadjimihalakis, P.M. *J. Heterocyclic. Chem.*, 1991, 28, 625., 13 g, 57.8 mmol) and acetic acid (150 mL) was added iron powder (9.6 g, 172.5 mmol) at room

temperature, then the mixture was refluxed for 30 min. After cooling, the mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (gradient elution from 1:1 to 1:2) to afford 3.22 g

(28%) of the title compound as orange solid: $^1\text{H-NMR}$ (CDCl_3) δ 7.67 (1H, s), 6.23 (1H, s), 5.85 (2H, br.s), 4.19-4.33 (4H, m).

STEP 2. 2-{4-[(7-Nitro-2,3-dihydro-1,4-benzodioxin-6-yl)amino]phenyl} ethanol

The title compound was prepared according to the procedure described in step 1 of Example 45 from 7-nitro-2,3-dihydro-1,4-benzodioxin-6-amine (step 1) and 4-bromophenylethyl alcohol.

$^1\text{H-NMR}$ (CDCl_3) δ 7.77 (1H, s), 7.26 (2H, d, $J=8.4$ Hz), 7.19 (2H, d, $J=8.4$ Hz), 6.64 (1H, s), 4.20-4.31 (4H, m), 3.89 (2H, t, $J=6.4$ Hz), 2.88 (2H, t, $J=6.4$ Hz).

STEP 3. 2-{4-[(7-Amino-2,3-dihydro-1,4-benzodioxin-6-yl)amino]phenyl} ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[(7-nitro-2,3-dihydro-1,4-benzodioxin-6-yl)amino]phenyl} ethanol (step 2).

$^1\text{H-NMR}$ (CDCl_3) δ 7.02-7.05 (2H, m), 6.62-6.65 (3H, m), 6.33 (1H, s), 5.00 (1H, br.s), 4.15-4.24 (4H, m), 3.79 (2H, t, $J=6.6$ Hz), 3.53 (2H, br.s), 2.76 (2H, t, $J=6.6$ Hz).

STEP 4. 2-[4-(2-Ethyl-6,7-dihydro-1H-[1,4]dioxino[2,3-f]benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(7-amino-2,3-dihydro-1,4-benzodioxin-6-

yl)amino]phenyl} ethanol (step 3) and propionyl chloride.

TLC R_f = 0.5 (hexane : ethyl acetate = 1:2).

STEP 5. 2-[4-(2-Ethyl-6,7-dihydro-1H-[1,4]dioxino[2,3-f]benzimidazol-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[(7-amino-2,3-dihydro-1,4-benzodioxin-6-

5 yl)amino]phenyl}ethyl propionate (step 4).

¹H-NMR (CDCl₃) δ 7.42 (2H, d, J=8.1 Hz), 7.25-7.28 (3H, m), 6.58 (1H, s), 4.21-4.27 (4H, m), 3.97 (2H, t, J=6.6 Hz), 2.98 (2H, t, J=6.6 Hz), 2.74 (2H, q, J=7.3 Hz), 1.31 (3H, t, J=7.3 Hz).

STEP 6. 1-[4-(2-Chloroethyl)phenyl]-2-ethyl-6,7-dihydro-1H-[1,4]dioxino[2,3-f]benzimidazole

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The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-6,7-dihydro-1H-[1,4]dioxino[2,3-f]benzimidazol-1-yl)phenyl]ethanol (step 5).

¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.1 Hz), 7.26-7.39 (3H, m), 6.58 (1H, s), 4.25
15 (4H, s), 3.80 (2H, t, J=7.3 Hz), 3.20 (2H, t, J=7.3 Hz), 2.74 (2H, q, J=7.6 Hz), 1.31 (3H, t, J=7.6 Hz).

STEP 7. 2-[4-(2-Ethyl-6,7-dihydro-1H-[1,4]dioxino[2,3-f]benzimidazol-1-yl)phenyl]ethyl azide

The title compound was prepared according to the procedure described in step 8
20 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-6,7-dihydro-1H-[1,4]dioxino[2,3-f]benzimidazole (step 6).

¹H-NMR (CDCl₃) δ 7.40 (2H, d, J=8.3 Hz), 7.24-7.29 (3H, m), 6.57 (1H, s), 4.21-4.26 (4H, m), 3.59 (2H, t, J=7.0 Hz), 2.99 (2H, t, J=7.0 Hz), 2.73 (2H, q, J=7.5 Hz), 1.30 (3H, t, J=7.5 Hz).

STEP 8. 2-[4-(2-Ethyl-6,7-dihydro-1H-[1,4]dioxino[2,3-f]benzimidazol-1-yl)phenyl]ethylamine

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The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(2-ethyl-6,7-dihydro-1*H*-[1,4]dioxino[2,3-*f*]benzimidazol-1-yl)phenyl]ethyl azide (step 6).

¹H-NMR (CDCl₃) δ 77.40 (2H, d, J=8.3 Hz), 7.24-7.27 (3H, m), 6.62 (1H, s), 4.21 (4H, s), 3.24-3.26 (2H, m), 3.11 (2H, t, J=6.9 Hz), 2.72 (2H, q, J=7.4 Hz), 1.30 (3H, t, J=7.4 Hz).

STEP 9. 2-Ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-6,7-dihydro-1*H*-[1,4]dioxino[2,3-*f*]benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-ethyl-6,7-dihydro-1*H*-[1,4]dioxino[2,3-*f*]benzimidazol-1-yl)phenyl]ethylamine (step 8).

MS (ESI) *m/z* 521 (M + H)⁺; ¹H-NMR (CDCl₃) δ 7.76 (2H, d, J=8.4 Hz), 7.18-7.31 (7H, m), 6.64 (1H, br.s), 6.56 (1H, br.s), 4.24 (4H, s), 3.56 (2H, t, J=6.9 Hz), 2.90 (2H, t, J=6.9 Hz), 2.70 (2H, q, J=7.6 Hz), 2.41 (3H, s), 1.27 (3H, t, J=7.6 Hz).

EXAMPLE 117

2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-6,7-DIHYDRO-1*H*-[1,4]DIOXINO[2,3-*f*]BENZIMIDAZOLE, SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-6,7-dihydro-1*H*-[1,4]dioxino[2,3-*f*]benzimidazole (Example 116).

mp 162-173 °C; ¹H-NMR (DMSO-*d*₆) δ 7.83 (2H, d, J=8.0 Hz), 7.58 (2H, d, J=8.6 Hz), 7.54 (2H, d, J=8.0 Hz), 7.35 (2H, d, J=8.6 Hz), 7.29 (1H, s), 6.68

(1H, s), 4.42 (4H, s), 3.38 (2H, br.s), 2.94 (2H, t, J=6.9 Hz), 2.86 (2H, q, J=7.6 Hz), 2.49 (3H, s), 1.39 (3H, t, J=7.6 Hz); IR (KBr) ν_{max} 3360, 2875, 1596, 1516, 1468, 1335, 1167, 1130, 1064, 920 cm^{-1} .

EXAMPLE 118-EXAMPLE 161

- 5 The compounds disclosed hereinafter were prepared according to the following procedure: To a solution of requisite commercially available sulfonamide (0.05 mmol) in DMF (1 mL) was added a suspension of NaH (0.1 mmol) in DMF (0.5 mL) and the mixture was shaken for 5 min. To this mixture was added a solution of phenyl 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-
- 10 yl)phenyl]ethylcarbamate (step 1 of Example 18, 7 mg, 0.05 mmol) in DMF (0.5 mL), and the mixture was shaken at room temperature for 30 min. After removal of DMF by nitrogen blow, the residue was dissolved in water (3 mL) and loaded onto a 0.5g/3mL BondElute SCX. The solid phase was washed with MeOH (5 mL), and then eluted with 10% HCl/MeOH (3 mL). The eluate was
- 15 concentrated under reduced pressure to give the title compound.

EXAMPLE 118

3-(4-{2-[{(3,4-

DICHLOROPHENYL)SULFONYL]AMINO}CARBONYL]AMINO}ETHYL}PHE-
NYL)-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,

- 20 HYDROCHLORIDE

MS (ESI) m/z 546.6 (M + H)⁺.

EXAMPLE 119

2-ETHYL-3-{4-[2-{[(3-

- NITROPHENYL)SULFONYL]AMINO}CARBONYL]AMINO}ETHYL]PHE-
25 NYL)-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, HYDROCHLORIDE

MS (ESI) m/z 523.3 (M + H)⁺.

EXAMPLE 120

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3-(4-{2-[(4-
CHLOROPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE,
HYDROCHLORIDE

- 5 MS (ESI) m/z 512.5 (M + H)⁺.

EXAMPLE 121

2-ETHYL-3-[4-[2-{(4-
NITROPHENYL)SULFONYL]AMINO}CARBONYL]AMINO]ETHYL]PHE
NYL]-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

- 10 MS (ESI) m/z 523.3 (M + H)⁺.

EXAMPLE 122

N-[4-{[(2-[4-(2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDIN-3-
YL)PHENYL]ETHYL}AMINO)CARBONYL]AMINO}SULFONYL]PHENY
L]-2,2-DIMETHYLPROPANAMIDE, HYDROCHLORIDE

- 15 MS (ESI) m/z 577.5 (M + H)⁺.

EXAMPLE 123

3-(4-{2-[(4-
CHLOROPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE,
HYDROCHLORIDE

- 20 HYDROCHLORIDE

MS (ESI) m/z 512.4 (M + H)⁺.

EXAMPLE 124

3-(4-{2-[(4-
CHLOROPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE,
HYDROCHLORIDE

- 25 HYDROCHLORIDE

MS (ESI) m/z 512.5 (M + H)⁺.

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EXAMPLE 125

3-(4-{2-[({[(5-CHLORO-2-THIENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-*b*]PYRIDINE,

5 HYDROCHLORIDE

MS (ESI) *m/z* 518.6 (M + H)⁺.

EXAMPLE 126

3-(4-{2-[({[(5-BROMO-2-THIENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-*b*]PYRIDINE,

10 HYDROCHLORIDE

MS (ESI) *m/z* 564.2 (M + H)⁺.

EXAMPLE 127

2-ETHYL-3-{4-[2-({[(2-METHYL-5-NITRO-PHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-5,7-DIMETHYL-3H-IMIDAZO[4,5-*b*]PYRIDINE, HYDROCHLORIDE

15 MS (ESI) *m/z* 537.3 (M + H)⁺.EXAMPLE 128

3-(4-{2-[({[(3,4-DIMETHOXYPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-*b*]PYRIDINE, HYDROCHLORIDE

20 MS (ESI) *m/z* 538.4 (M + H)⁺.EXAMPLE 129

3-(4-{2-[({[(4-BUTYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHE

25

NYL)-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,
HYDROCHLORIDE

MS (ESI) m/z 534.5 ($M + H$)⁺.

EXAMPLE 130

- 5 2-ETHYL-3-(4-{2-[(4-
METHOXYPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}
PHENYL)-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,
HYDROCHLORIDE

MS (ESI) m/z 508.4 ($M + H$)⁺.

10 EXAMPLE 131

2-ETHYL-5,7-DIMETHYL-3-[4-(2-{[(5-(PHENYLSULFANYL)-2-
THIENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL)PHENYL]-
3*H*-IMIDAZO[4,5-*b*]PYRIDINE, HYDROCHLORIDE

MS (ESI) m/z 592.4 ($M + H$)⁺.

15 EXAMPLE 132

3-(4-{2-[(3,5-
DICHLOROPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}
PHENYL)-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,
HYDROCHLORIDE

- 20 MS (ESI) m/z 546.6 ($M + H$)⁺.

EXAMPLE 133

3-(4-{2-[(2-
BROMOPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PH
ENYL)-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,
HYDROCHLORIDE

- 25 HYDROCHLORIDE

MS (ESI) m/z 558.0 ($M + H$)⁺.

EXAMPLE 134

3-(4-{2-[(4,5-DICHLORO-2-THIENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

5 MS (ESI) m/z 552.6 (M + H)⁺.

EXAMPLE 135

3-[4-(2-{[(2-(2,4-DICHLOROPHENOXY)PHENYL]SULFONYL}AMINO)CARBONYL)AMINO}ETHYL)PHENYL]-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

10 MS (ESI) m/z 638.8 (M + H)⁺.

EXAMPLE 136

3-(4-{2-[(5-CHLORO-1,3-DIMETHYL-1H-PYRAZOL-4-YL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

15 MS (ESI) m/z 530.3 (M + H)⁺.

EXAMPLE 137

3-(4-{2-[(2,4-DIMETHYL-1,3-THIAZOL-5-YL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

20 MS (ESI) m/z 523.2 (M + H)⁺.

EXAMPLE 138

3-(4-{2-[(4-CYANOPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHE

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NYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE,
HYDROCHLORIDE

MS (ESI) m/z 503.2 (M + H)⁺.

EXAMPLE 139

- 5 3-(4-{2-[(3,4-DIFLUOROPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}
PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE,
HYDROCHLORIDE

MS (ESI) m/z 514.3 (M + H)⁺.

- 10 EXAMPLE 140

3-(4-{2-[(2,5-DICHLORO-3-THIENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-
2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE,
HYDROCHLORIDE

- 15 MS (ESI) m/z 552.3 (M + H)⁺.

EXAMPLE 141

N-[5-[(2-[4-(2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDIN-3-
YL)PHENYL]ETHYL}AMINO)CARBONYL]AMINO}SULFONYL)-1,3,4-
THIADIAZOL-2-YL]ACETAMIDE, HYDROCHLORIDE

- 20 MS (ESI) m/z 543.0 (M + H)⁺.

EXAMPLE 142

3-{4-[2-[(4-CHLORO-3-NITROPHENYL)SULFONYL]AMINO]CARBONYL}AMINO}ETHYL]PHE
NYL}-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE,
HYDROCHLORIDE

- 25 HYDROCHLORIDE

MS (ESI) m/z 557.2 (M + H)⁺.

EXAMPLE 143

105101*15222660

3-(4-{2-[(4-BUTOXYPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

5 MS (ESI) m/z 550.4 (M + H)⁺.

EXAMPLE 144

3-[4-(2-{[(2,6-DICHLORO-4-(TRIFLUOROMETHYL)PHENYL]SULFONYL}AMINO)CARBONYL]AMINO}ETHYL)PHENYL]-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

10

MS (ESI) m/z 614.4 (M + H)⁺.

EXAMPLE 145

3-[4-(2-{[(4-(1-ADAMANTYL)PHENYL]SULFONYL}AMINO)CARBONYL]AMINO}ETHYL)PHENYL]-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

15

MS (ESI) m/z 612.4 (M + H)⁺.

EXAMPLE 146

3-(4-{2-[(4,5-DIBROMO-2-THIENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

20

MS (ESI) m/z 642.0 (M + H)⁺.

EXAMPLE 147

2-ETHYL-5,7-DIMETHYL-3-[4-(2-{[(5-(2-THIENYLSULFANYL)-2-THIENYL]SULFONYL}AMINO)CARBONYL]AMINO}ETHYL)PHENYL]-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

25

MS (ESI) m/z 598.2 (M + H)⁺.

EXAMPLE 148

3-(4-{2-[(4-TERT-

BUTYLPHENYL)SULFONYL}AMINO}CARBONYL)AMINO}ETHYL}PHE

5 NYL)-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,

HYDROCHLORIDE

MS (ESI) m/z 534.4 (M + H)⁺.

EXAMPLE 149

3-(4-{2-[(4-AMINO-3-

10 CHLOROPHENYL)SULFONYL}AMINO}CARBONYL)AMINO}ETHYL}PH

ENYL)-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,

HYDROCHLORIDE

MS (ESI) m/z 527.3 (M + H)⁺.

EXAMPLE 150

15 2-ETHYL-5,7-DIMETHYL-3-(4-{2-[(2,4,5-

TRICHLOROPHENYL)SULFONYL}AMINO}CARBONYL)AMINO}ETHYL

}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, HYDROCHLORIDE

MS (ESI) m/z 580.4 (M + H)⁺.

EXAMPLE 151

20 3-(4-{2-[(2,5-

DIMETHOXYPHENYL)SULFONYL}AMINO}CARBONYL)AMINO}ETHY

L}PHENYL)-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,

HYDROCHLORIDE

MS (ESI) m/z 538.3 (M + H)⁺.

25 EXAMPLE 152

3-(4-{2-[(6-ETHOXY-1,3-BENZOTHAZOL-2-

YL)SULFONYL}AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-

ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,
HYDROCHLORIDE

MS (ESI) m/z 579.1 ($M + H$)⁺.

EXAMPLE 153

- 5 3-(4-{2-[(5-(2-AMINO-4-
CHLOROPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL)PH
ENYL)-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,
HYDROCHLORIDE

MS (ESI) m/z 527.2 ($M + H$)⁺.

- 10 EXAMPLE 154

2-ETHYL-5,7-DIMETHYL-3-[4-(2-{[(5-(2-THIENYLSULFONYL)-2-
THIENYL]SULFONYL}AMINO)CARBONYL]AMINO}ETHYL)PHENYL]-
3*H*-IMIDAZO[4,5-*b*]PYRIDINE, HYDROCHLORIDE

MS (ESI) m/z 630.2 ($M + H$)⁺.

- 15 EXAMPLE 155

3-[4-(2-{[(2-CHLORO-5-
(TRIFLUOROMETHYL)PHENYL]SULFONYL}AMINO)CARBONYL)AMI
NO}ETHYL)PHENYL]-2-ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-
b]PYRIDINE, HYDROCHLORIDE

- 20 MS (ESI) m/z 580.2 ($M + H$)⁺.

EXAMPLE 156

3-{4-[2-{[(2,3-DIHYDRO-1,4-BENZODIOXIN-6-
YLSULFONYL)AMINO}CARBONYL]AMINO}ETHYL]PHENYL}-2-
ETHYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDINE,

- 25 HYDROCHLORIDE

MS (ESI) m/z 536.2 ($M + H$)⁺.

EXAMPLE 157

2-ETHYL-5,7-DIMETHYL-3-[4-(2-{[(2-(
(PHENYLSULFANYL)PHENYL]SULFONYL}AMINO)CARBONYL]AMINO)
O}ETHYL)PHENYL]-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE
MS (ESI) m/z 586.3 (M + H)⁺.

5 EXAMPLE 158

3-(4-{2-[[(4-CHLORO-2,5-
DIMETHYLPHENYL]SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}
PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE,
HYDROCHLORIDE

10 MS (ESI) m/z 540.3 (M + H)⁺.

EXAMPLE 159

3-(4-{2-[[(3-BROMO-5-CHLORO-2-
THIENYL]SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-
2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE,

15 HYDROCHLORIDE

MS (ESI) m/z 598.1 (M + H)⁺.

EXAMPLE 160

2-ETHYL-5,7-DIMETHYL-3-(4-{2-[[(4-
VINYLPHENYL]SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHE
NYL)-3H-IMIDAZO[4,5-b]PYRIDINE, HYDROCHLORIDE

20 MS (ESI) m/z 504.4 (M + H)⁺.

EXAMPLE 161

METHYL 2,4-DICHLORO-5-({[(2-[4-(2-ETHYL-5,7-DIMETHYL-3H-
IMIDAZO[4,5-b]PYRIDIN-3-
YL)PHENYL]ETHYL}AMINO)CARBONYL]AMINO}SULFONYL)BENZO
ATE, HYDROCHLORIDE

25 MS (ESI) m/z 604.5 (M + H)⁺.

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EXAMPLE 162-Example 194

The compounds disclosed hereinafter were prepared according to the following procedure: To a mixture of requisite commercially available carbonic acid and dichloromethane was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,

- 5 hydrochloride (WSC) (0.05 mmol, 0.5 mL), then to the reaction mixture was added a solution of 3-amino-4,6-dimethyl-2-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}anilino)pyridine* (0.038 mmol) in dichloromethane (0.5 mL) at room temperature. The reaction mixture was stirred for 3 days at room temperature, then stirred for an additional 1 day at
- 10 40 °C. After removal of the solvent, the residue was dissolved in MeOH (1 mL) and the solution was filtered through a membrane filter. The filtrate was purified by preparative LC/MS (Shiseido capcell pack UG80 C18 (4.6 x 50mm) eluting with MeOH/0.1%HCOOH (v/v, 20/80 to 90/10)) to give the title compound.

- *3-Amino-4,6-dimethyl-2-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}anilino)pyridine was
- 15 prepared as follows;

STEP 1, 3-{4-[(4,6-Dimethyl-3-nitro-2-pyridinyl)amino]phenyl}propanoic acid

- To a solution of 2-chloro-4,6-dimethyl-3-nitropyridine (17.9 g, 96 mmol) and methyl 3-(4-aminophenyl)propanoate (19 g, 96 mmol) in DMSO (100 mL) was
- 20 added *N,N*-diisopropylethylamine (26 g, 200 mmol), and the reaction mixture was heated at 140 °C overnight. The reaction mixture was partitioned between water (400 mL) and ethyl acetate/toluene (v/v, 2:1, 300 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate/toluene (v/v, 2:1, 200 mL). The combined organic extracts were washed with brine (200
- 25 mL), dried (Na₂SO₄), and concentrated. To a solution of residual oil in methanol (100 mL) was added 2 *N* aqueous NaOH (150 mL, 300 mmol) and the resulting mixture was stirred at room temperature for 2 h. The volatile component was

removed under reduced pressure and the residue was washed with ethyl acetate (200 mL). The aqueous phase was acidified with 2N hydrochloric acid (200 mL, 400 mmol) and extracted with ethyl acetate (3 x 200 mL). The extracts were washed with brine (200 mL), dried (Na_2SO_4), and concentrated to give 23.2 g (77%) of the title compound as pale brown solids.

$^1\text{H-NMR}$ (CDCl_3) δ : 9.57 (1H, s), 7.56 (2H, d, $J=8.4$ Hz), 7.19 (2H, d, $J=8.4$ Hz), 6.52 (1H, s), 2.95 (2H, t, $J=7.5$ Hz), 2.66 (2H, t, $J=7.5$ Hz), 2.55 (3H, s), 2.43 (3H, s).

STEP 2, Phenyl 2-{4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}ethylcarbamate

To a stirred solution of 3-{4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}propanoic acid (step 1, 10 g, 31.7 mmol) in dioxane (200 mL) was added diphenylphosphoryl azide (DPPA) (7.54 mL, 35 mmol) and triethylamine (4.87 mL, 35 mmol). The reaction mixture was heated at 120 °C for 2 h. To the reaction mixture was added phenol (6.6 g, 70 mmol) and the reaction mixture was refluxed. After 3 h, to the reaction mixture was added an additional amount of phenol (3.3 g, 35 mmol). The resulting mixture was heated under reflux temperature overnight. The volatile component was removed and the residue was partitioned between aqueous 10% aqueous citric acid (200 mL) and ethyl acetate (300 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (300 mL). The combined organic extracts were washed with water (300 mL) and brine (300 mL), then dried (Na_2SO_4), and concentrated. The crude product was purified by flash column chromatography on silica gel eluting with hexane/EtOAc (2:1) to afford 10.3 g (77%) of the title compound as orange solids.

¹H-NMR (CDCl₃) δ: 9.60 (1H, s), 7.61 (2H, d, J=8.6 Hz), 7.38-7.32 (2H, m), 7.24-7.16 (3H, m), 7.14-7.09 (2H, m), 6.54 (1H, s), 5.06 (1H, br.s), 3.58-3.50 (2H, m), 2.89 (2H, t, J=6.9 Hz), 2.56 (3H, s), 2.44 (3H, s).

STEP 3, 4,6-Dimethyl-2-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}anilino)-3-nitropyridine

To a stirred solution of phenyl 2-{4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}ethylcarbamate (step 2, 10.0 g, 24.6 mmol) and *p*-toluenesulfonamide (6.3 g, 36.8 mmol) in DMF (100mL) was added sodium hydride (2.0 g, 50 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water (300 mL) and extracted with ethyl acetate/toluene (v/v, 2:1, 2x 300 mL). The organic extracts were washed with water (100 mL) and brine (200 mL), then dried (Na₂SO₄). Removal of the solvent gave crude product. Recrystallization from ethyl acetate gave 9.6 g (81%) of the title compound as brown solids. The mother liquor was concentrated and the residue was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to afford 1.9 g (16%) of the title compound as brown solids.

¹H-NMR (CDCl₃) δ: 9.75 (1H, s), 7.62 (2H, d, J=8.4 Hz), 7.59 (2H, d, J=8.4 Hz), 7.26 (2H, d, J=8.4 Hz), 7.15 (2H, d, J=8.4 Hz), 6.62-6.50 (2H, m), 3.55-3.42 (2H, m), 2.80 (2H, t, J=6.9 Hz), 2.56 (3H, s), 2.43 (3H, s), 2.39 (3H, s).

STEP 4, 3-Amino-4,6-dimethyl-2-(4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}anilino)pyridine

To a solution of 4,6-dimethyl-2-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}anilino)-3-nitropyridine (step 3, 11.4 g, 23.6 mmol) in methanol (250 mL) was added 10% Pd-C (2.0 g). The resulting mixture was stirred under the medium pressure of hydrogen (4.0 kgf/cm²) for 4 h. The catalyst was removed by filtration, and the filtrate was

concentrated. The residue was recrystallized from ethyl acetate to afford 9.0 g (85%) of the title compound as off white solids.

¹H-NMR (CDCl₃) δ: 7.69 (2H, d, J=8.0 Hz), 7.26 (2H, d, J=8.0 Hz), 7.00-6.95 (4H, m), 6.61 (1H, s), 6.24 (1H, br.s), 3.44-3.38 (2H, m), 2.70 (2H, t, J=6.7 Hz), 2.39 (3H, s), 2.33 (3H, s), 2.19 (3H, s).

EXAMPLE 162

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-[3-OXO-3-(2-THIENYL)PROPYL]-3H-IMIDAZO[4,5-

b]PYRIDINE, FORMATE

MS (ESI) m/z 602.48 (M + H)⁺.

EXAMPLE 163

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-(PHENOXYMETHYL)-3H-IMIDAZO[4,5-b]PYRIDINE,

FORMATE

MS (ESI) m/z 570.5 (M + H)⁺.

EXAMPLE 164

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-[2-(3-PYRIDINYL)ETHYL]-3H-IMIDAZO[4,5-b]PYRIDINE,

FORMATE

MS (ESI) m/z 569.49 (M + H)⁺.

EXAMPLE 165

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-[2-(3-PYRIDINYL)ETHYL]-3H-IMIDAZO[4,5-b]PYRIDINE,

ENYL)-2-(3-OXO-3-PHENYLPROPYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE

MS (ESI) m/z 596.28 (M + H)⁺.

EXAMPLE 166

- 5 5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-(3-PHENYLPROPYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE
MS (ESI) m/z 582.52 (M + H)⁺.

EXAMPLE 167

- 10 2-(ETHOXYMETHYL)-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE
MS (ESI) m/z 522.46 (M + H)⁺.

EXAMPLE 168

- 15 5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-[(PHENYLSULFANYL)METHYL]-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE
MS (ESI) m/z 586.49 (M + H)⁺.

- 20 EXAMPLE 169

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-PENTYL-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE
MS (ESI) m/z 534.51 (M + H)⁺.

- 25 EXAMPLE 170

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T0510T-19772660

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-(2-PHENYLETHYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE
MS (ESI) m/z 568.51 (M + H)⁺.

5 EXAMPLE 171

2-(3-BUTYNYL)-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE
MS (ESI) m/z 516.45 (M + H)⁺.

10 EXAMPLE 172

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-(3-THIENYLMETHYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

15 MS (ESI) m/z 560.44 (M + H)⁺.EXAMPLE 173

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-(4-PENTYNYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

20 MS (ESI) m/z 530.46 (M + H)⁺.EXAMPLE 174

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-(2-THIENYLMETHYL)-3H-IMIDAZO[4,5-b]PYRIDINE,

25 FORMATEMS (ESI) m/z 560.44 (M + H)⁺.EXAMPLE 175

10501-792260

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-(3-PYRIDINYLMETHYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE

- 5 MS (ESI) m/z 555.48 (M + H)⁺.

EXAMPLE 176

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-[(2E)-2-PENTENYL]-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE

- 10 MS (ESI) m/z 532.48 (M + H)⁺.

EXAMPLE 177

2-BENZYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE

- 15 MS (ESI) m/z 554.48 (M + H)⁺.

EXAMPLE 178

2-(CYANOMETHYL)-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE

- 20 MS (ESI) m/z 503.41 (M + H)⁺.

EXAMPLE 179

2-(METHOXYMETHYL)-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE

- 25 MS (ESI) m/z 508.44 (M + H)⁺.

EXAMPLE 180

0997761.101501

2-HEPTYL-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE
MS (ESI) m/z 562.33 (M + H)⁺.

5 EXAMPLE 181

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-OCTYL-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE
MS (ESI) m/z 576.37 (M + H)⁺.

10 EXAMPLE 182

5,7-DIMETHYL-2-(4-METHYLPENTYL)-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE
MS (ESI) m/z 548.53 (M + H)⁺.

15 EXAMPLE 183

2-[(BENZYLOXY)METHYL]-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE
MS (ESI) m/z 584.52 (M + H)⁺.

20 EXAMPLE 184

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-(2-PHENOXYETHYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE, FORMATE

25 MS (ESI) m/z 584.33 (M + H)⁺.EXAMPLE 185

0997761-101501

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-[3-(2-THIENYL)PROPYL]-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

- 5 MS (ESI) m/z 588.5 ($M + H$)⁺.

EXAMPLE 186

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-(2-NAPHTHYLMETHYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

- 10

MS (ESI) m/z 604.37 ($M + H$)⁺.

EXAMPLE 187

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-(4-PHENYLBUTYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

- 15

MS (ESI) m/z 596.42 ($M + H$)⁺.

EXAMPLE 188

5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-2-(5-PHENYLPENTYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

- 20

MS (ESI) m/z 610.45 ($M + H$)⁺.

EXAMPLE 189

2-(2-ETHOXYETHYL)-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

- 25

MS (ESI) m/z 536.38 ($M + H$)⁺.

EXAMPLE 190

0997751.101501

2-(2,3-DIHYDRO-1H-INDEN-2-YLMETHYL)-5,7-DIMETHYL-3-(4-{2-
[({[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

- 5 MS (ESI) m/z 594.45 (M + H)⁺.

EXAMPLE 191

2-(CYCLOPROPYLMETHYL)-5,7-DIMETHYL-3-(4-{2-[(({[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

- 10 MS (ESI) m/z 518.45 (M + H)⁺.

EXAMPLE 192

5,7-DIMETHYL-3-(4-{2-[(({[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-2-[2-(METHYLSULFANYL)ETHYL]-3H-IMIDAZO[4,5-
b]PYRIDINE, FORMATE

- 15

MS (ESI) m/z 538.44 (M + H)⁺.

EXAMPLE 193

2-HEXYL-5,7-DIMETHYL-3-(4-{2-[(({[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

- 20 MS (ESI) m/z 548.44 (M + H)⁺.

EXAMPLE 194

5,7-DIMETHYL-3-(4-{2-[(({[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-2-(4-PENTENYL)-3H-IMIDAZO[4,5-b]PYRIDINE, FORMATE

- 25 MS (ESI) m/z 532.42 (M + H)⁺.

EXAMPLE 195

0997761-101501

6-CHLORO-5-CYANO-2-ETHYL-1-[4-{2-[(4-METHYLPHENYLSULFONYL)AMINO]CARBONYL}AMINO]ETHYL}PHENYL]-1H-BENZIMIDAZOLE

STEP 1. 6-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-5-

5 carbonitrile

The reaction was carried out according to the procedure described in step 7 of Example 1 from 6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazole-5-carbonitrile (Example 111, step 4).

- ¹H-NMR (CDCl₃) δ 8.07 (1H, s), 7.50 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 7.19 (1H, s), 3.83 (2H, t, J=7.1 Hz), 3.22 (2H, t, J=7.1 Hz), 2.79 (2H, q, J=7.5 Hz), 1.37 (3H, t, J=7.5 Hz).

STEP 2. 1-[4-(2-Azidoethyl)phenyl]-6-chloro-2-ethyl-1H-benzimidazole-5-carbonitrile

The reaction was carried out according to the procedure described in step 8 of

- 15 Example 1 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-5-carbonitrile (step 1).

¹H-NMR (CDCl₃) δ 8.07 (1H, s), 7.49 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.18 (1H, s), 3.64 (2H, t, J=7.0 Hz), 3.04 (2H, t, J=7.0 Hz), 2.79 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

- 20 STEP 3. 1-[4-(2-Aminoethyl)phenyl]-6-chloro-2-ethyl-1H-benzimidazole-5-carbonitrile

The reaction was carried out according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1H-benzimidazole-5-carbonitrile (step 2).

- 25 ¹H-NMR (CDCl₃) δ 8.06 (1H, s), 7.46 (2H, d, J=8.1 Hz), 7.26 (2H, d, J=8.1 Hz), 7.19 (1H, s), 3.09 (2H, t, J=7.1 Hz), 2.89 (2H, t, J=7.1 Hz), 2.79 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

STEP 4. 6-Chloro-5-cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole

The reaction was carried out according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1H-

5 benzimidazole-5-carbonitrile (step 3).

mp 219-224 °C; IR (KBr) v: 3388, 2229, 1708, 1618, 1514, 1466, 1344, 1161, 1089 cm⁻¹.

MS (ESI) m/z 522 (M+H)⁺, 520 (M-H)⁻; ¹H-NMR (DMSO-d₆) δ 8.38 (1H, s), 7.77 (2H, d, J=8.2 Hz), 7.31-7.49 (6H, m), 7.32 (1H, s), 6.53 (1H, br.s), 3.26-3.28 (2H, m), 2.69-2.81 (4H, m), 2.35 (3H, s), 1.25 (3H, t, J=7.6 Hz).

10 THE SYNTHETIC PROCEDURE OF EXAMPLE 196-EXAMPLE 197

The compounds disclosed hereinafter were prepared according to the following procedure: To a mixture of requisite commercially available carbonic acid and dichloromethane (DCM) was added 1-ethyl-3-(3-

15 dimethylaminopropyl)carbodiimide, hydrochloride (WSC) (0.05 mmol, 0.5 mL) followed by a solution of 3-amino-4,6-dimethyl-2-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}anilino)pyridine (0.038 mmol) in DCM (0.5 mL) at room temperature. The reaction mixture was stirred

for 3 days at room temperature, then stirred for an additional day at 40 °C. After removal of the solvent, the residue was dissolved in MeOH (1 mL) and the solution was filtered through a membrane filter. The filtrate was purified by preparative LC/MS (Shiseido capcell pack UG80 C18 (20 x 50 mm) eluting with MeOH/0.1%HCOOH (v/v, 20/80 to 90/10) to give the title compound.

EXAMPLE 196

25 N-{{[(2-{4-[5,7-DIMETHYL-2-(4-METHYLPENTYL)-3H-IMIDAZO[4,5-b]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) m/z 548.53 ($M + H$)⁺.

EXAMPLE 197

N-{[(2-{4-[5,7-DIMETHYL-2-(3-OXO-3-PHENYLPROPYL)-3*H*-
IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-
4-METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) m/z 596.28 ($M + H$)⁺.

THE SYNTHETIC PROCEDURE OF EXAMPLE 198-EXAMPLE 216

The compounds disclosed hereinafter were prepared according to the following procedure: The carboxylic acid (0.06 mmol) was dissolved with *N,N*-diisopropylethylamine (DIEA) (0.106 mmol) and dichloromethane (DCM) (0.3 mL). To this mixture was added 1-hydroxybenzotriazole hydrate (HOBt) (0.06 mmol) in *N,N*-dimethylformamide (DMF) (0.02 mL). To the reaction were added 3-amino-4, 6-dimethyl-2-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino} ethyl} anilino)pyridine (0.044 mmol) in DCM (0.3 mL) and DMF (0.08 mL), then *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) (0.13 mmol) in DMF (0.25 mL). The reaction solution was stirred for 6hr at room temperature, then heated at 40 °C over night. After removal of the solvent, the residue was dissolved in MeOH (0.8 mL). The solution was loaded onto a Varian BondElute® SCX cartridge (500 mg/3 mL) which was preconditioned with 2 mL of MeOH. The solid-phase matrix was washed with 5 mL of MeOH and then eluted with 2N ammonia/MeOH (3 mL). After the removal of solvent, the product was used for the next step reaction.

The intermediate product of 1st step was dissolved with EtOH (2 mL), then to the reaction solution was added excess 2N aq.NaOH (1 mL). The reaction mixture was stirred at 40 °C to 70 °C over night. After the reaction finished, the solvent was removed. To the residue was added 2N aq.HCl (1 mL,

adjusted with pH 7.0). The aqueous layer was extracted with DCM (1 mL X 3). The organic layer was concentrated to afford the residue. The crude product was purified by preparative LC/MS (Shiseido capcellpack UG 80 C18 (20 x 50mm) eluting with MeOH/0.1%HCOOH (v/v, 20/80 to 90/10) to give the title

5 compound as a formate.

EXAMPLE 198

N-{5-[5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO} CARBONYL)AMINO]ETHYL}PHENYL}-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-2-YL]PENTYL}ACETAMIDE,

10 FORMATE

MS (ESI) *m/z* 591.33 (M + H)⁺.

EXAMPLE 199

N-{[(2-{4-[5,7-DIMETHYL-2-(5-OXO-5-PHENYLPENTYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-

15 4-METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) *m/z* 624.37 (M + H)⁺.

EXAMPLE 200

N-{[(2-{4-[2-(2-CYCLOPENTEN-1-YLMETHYL)-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-

20 4-METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) *m/z* 544.40 (M + H)⁺.

EXAMPLE 201

N-{[(2-{4-[2-(1-CYCLOPENTEN-1-YLMETHYL)-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-

25 4-METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) *m/z* 544.40 (M + H)⁺.

EXAMPLE 202

(2Z)-3-[5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL]-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-2-YL]-*N*-PROPYL-2-PROPENAMIDE, FORMATE

- 5 MS (ESI) m/z 575.44 ($M + H$)⁺.

EXAMPLE 203

N-{[(2-{4-[5,7-DIMETHYL-2-(1-METHYL-3-OXO-3-PHENYLPROPYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL}PHENYL}ETHYL)AMINO]CARBONYL)-4-METHYLBENZENESULFONAMIDE, FORMATE

- 10 MS (ESI) m/z 610.49 ($M + H$)⁺.

EXAMPLE 204

N-{[(2-{4-[5,7-DIMETHYL-2-(3,3,3-TRIFLUORO-2-METHYLPROPYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL}PHENYL}ETHYL)AMINO]CARBONYL)-4-METHYLBENZENESULFONAMIDE, FORMATE

- 15 MS (ESI) m/z 574.43 ($M + H$)⁺.

EXAMPLE 205

N-{[(2-{4-{2-[2-(DIETHYLAMINO)ETHYL]-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL}PHENYL)ETHYL]AMINO}CARBONYL)-4-METHYLBENZENESULFONAMIDE, FORMATE

- 20 MS (ESI) m/z 563.49 ($M + H$)⁺.

EXAMPLE 206

N-{[(2-{4-{2-[2-(4-FLUOROPHENYL)ETHYL]-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL}PHENYL)ETHYL]AMINO}CARBONYL)-4-METHYLBENZENESULFONAMIDE, FORMATE

- 25 MS (ESI) m/z 586.46 ($M + H$)⁺.

EXAMPLE 207

3-[5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO} CARBONYL)AMINO]ETHYL}PHENYL]-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-2-YL]-*N,N*-DIETHYLPROPANAMIDE, FORMATE

- 5 MS (ESI) m/z 591.50 ($M + H$)⁺.

EXAMPLE 208

N-{[(2-[4-(5,7-DIMETHYL-2-TETRAHYDRO-3-FURANYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL)PHENYL]ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE, FORMATE

- 10 MS (ESI) m/z 534.41 ($M + H$)⁺.

EXAMPLE 209

N-{[(2-[4-[5,7-DIMETHYL-2-(1-METHYLBUTYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE, FORMATE

- 15 MS (ESI) m/z 534.45 ($M + H$)⁺.

EXAMPLE 210

N-{[(2-[4-[2-(CYCLOPENTYLMETHYL)-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE, FORMATE

- 20 MS (ESI) m/z 546.46 ($M + H$)⁺.

EXAMPLE 211

N-{[(2-[4-[5,7-DIMETHYL-2-(2-METHYLCYCLOPROPYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE, FORMATE

- 25 MS (ESI) m/z 518.41 ($M + H$)⁺.

EXAMPLE 212

0997761.10501

N-[({2-[4-(5,7-DIMETHYL-2-{3-[4-(METHYLOXY)PHENYL]-3-OXOPROPYL}-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL)PHENYL]ETHYL}AMINO)CARBONYL]-4-METHYLBENZENESULFONAMIDE, FORMATE

- 5 MS (ESI) m/z 626.45 (M + H)⁺.

EXAMPLE 213

N-([2-(4-{2-[3-(3,4-DIMETHYLPHENYL)PROPYL]-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL}PHENYL)ETHYL)AMINO}CARBONYL)-4-METHYLBENZENESULFONAMIDE, FORMATE

- 10 MS (ESI) m/z 610.28 (M + H)⁺.

EXAMPLE 214

N-([2-(4-{2-[2-(4-FLUOROPHENYL)ETHENYL]-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL}PHENYL)ETHYL)AMINO}CARBONYL)-4-METHYLBENZENESULFONAMIDE, FORMATE

- 15 MS (ESI) m/z 584.41 (M + H)⁺.

EXAMPLE 215

N-[({2-[4-(5,7-DIMETHYL-2-{(Z)-2-[2-(METHYLOXY)PHENYL]ETHENYL}-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL)PHENYL]ETHYL}AMINO)CARBONYL]-4-

- 20 METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) m/z 596.29 (M + H)⁺.

EXAMPLE 216

N-{[(2-{4-[2-(5-HEXYNYL)-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-

- 25 METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) m/z 544.33 (M + H)⁺.

THE SYNTHETIC PROCEDURE OF EXAMPLE 217-EXAMPLE 220

The compounds disclosed hereinafter were prepared according to the following procedure: To a solution of 3-amino-4,6-dimethyl-2-(4-{2-[(4-methylphenyl)sulfonyl]amino} carbonyl)amino}ethyl}anilino)pyridine (0.044 mmol) in dichloromethane (DCM) (0.2 mL) and DMF (0.05 mL) was added
5 pyridine (0.103 mmol) in DCM (0.2 mL), and excess of acid chloride (0.066 mmol-0.088 mmol) at room temperature. The reaction mixture was stirred at ambient temperature until the starting compound was disappeared (4-6 hr). After the reaction was stopped, to the reaction mixture was added MeOH (0.2 mL), then stirred for 1hr. The solvent was removed by vacuum centrifuge.

10 The residue, which was dissolved with MeOH (0.8 mL), was loaded onto a Varian BondElute® SCX cartridge (500 mg/3 mL) which was preconditioned with 2 mL of MeOH. The solid-phase matrix was washed with 5 mL of MeOH and then eluted with 2N ammonia/MeOH (3 mL). The eluate was concentrated *in vacuo* to provide the intermediate product.

15 The intermediate product of 1st step was dissolved with EtOH (2 mL), then to the reaction solution was added excess 2N aq.NaOH (1 mL). The reaction mixture was stirred at 70 °C over night. After the removal of solvent, to the residue was added 2N aq.HCl to neutralize. The aqueous layer was extracted with DCM (1 mL X 5 times). The organic layer was dried with sodium sulfate,
20 then concentrated. The crude product was purified by preparative LC/MS (Shiseido capcellpack UG 80 C18 (20 x 50 mm) eluting with MeOH/0.1%HCOOH (v/v, 20/80 to 90/10) to give the title compound as a formate.

EXAMPLE 217

25 4-METHYL-N-[(2-[4-(2,5,7-TRIMETHYL-3H-IMIDAZO[4,5-b]PYRIDIN-3-YL)PHENYL]ETHYL)AMINO]CARBONYL]BENZENESULFONAMIDE, FORMATE

MS (ESI) m/z 478.31 ($M + H$)⁺.

EXAMPLE 218

N-{[(2-[4-[2-(2,2-DIMETHYLPROPYL)-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-

- 5 METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) m/z 534.40 ($M + H$)⁺.

EXAMPLE 219

N-[(2-[4-(2-CYCLOBUTYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL)PHENYL]ETHYL)AMINO]CARBONYL]-4-

- 10 METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) m/z 518.38 ($M + H$)⁺.

EXAMPLE 220

N-[(2-[4-(2-CYCLOPENTYL-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-3-YL)PHENYL]ETHYL)AMINO]CARBONYL]-4-

- 15 METHYLBENZENESULFONAMIDE, FORMATE

MS (ESI) m/z 532.44 ($M + H$)⁺.

EXAMPLE 221

4-(6-CHLORO-2-ETHYL-5-TRIFLUOROMETHYL-1*H*-BENZIMIDAZOL-1-YL) PHENETHYL(4-METHYLPHENYL) SULFONYLCARBAMATE *P*-

- 20 TOLUENESULFONATE

A mixture of 4-(6-chloro-2-ethyl-5-trifluoromethyl-1*H*-benzimidazol-1-yl)phenethyl(4-methylphenyl)sulfonylcarbamate (Example 106, 150 mg, 0.265 mmol), *p*-toluenesulfonic acid (50.5 mg, 0.265 mmol) in acetone (3% H₂O, 0.3 ml) was stirred at room temperature for 16 h. The precipitated crystalline solids were filtered, washed with acetone (0.05 ml x5), and dried in vacuo at 40 °C for 2 h to afford 158 mg (81%) of the title compound as white solids.
m.p.: 234.8 °C.

¹H-NMR (CDCl₃) δ: 8.66 (1H, br.s), 8.35 (1H, s), 7.85 (2H, d, J=8.1 Hz), 7.81 (2H, d, J=8.4 Hz), 7.53 (2H, d, J=8.4 Hz), 7.39-7.35 (3H, m), 7.29 (2H, d, J=7.9 Hz), 7.19 (2H, d, J=7.9 Hz), 4.35 (2H, t, J=6.2 Hz), 3.13 (2H, q, J=7.6 Hz), 3.04 (2H, t, J=6.3 Hz), 2.42 (3H, s), 2.36 (3H, s), 1.43 (3H, t, J=7.4 Hz).

5 EXAMPLE 222

4-(6-CHLORO-2-ETHYL-5-TRIFLUOROMETHYL-1H-BENZIMIDAZOL-1-
YL) PHENETHYL(4-METHYLPHENYL) SULFONYLCARBAMATE
BENZENESULFONATE

The title compound was prepared according to the procedure described
10 in Example 221 from 4-(6-chloro-2-ethyl-5-trifluoromethyl-1H-benzimidazol-1-yl) phenethyl(4-methylphenyl) sulfonylcarbamate (Example 106).

m.p.: 194.9 °C.

¹H-NMR (CDCl₃) δ: 8.83 (1H, br.s), 8.39 (1H, s), 7.99-7.95 (2H, m), 7.81 (2H, d, J=8.4 Hz), 7.54 (2H, d, J=8.4 Hz), 7.41-7.36 (6H, m), 7.29 (2H, d, J=8.4 Hz),
15 4.34 (2H, t, J=6.1 Hz), 3.14 (2H, q, J=7.6 Hz), 3.03 (2H, t, J=6.1 Hz), 2.41 (3H, s), 1.42 (3H, t, J=7.4 Hz).

EXAMPLE 223

4-(6-CHLORO-2-ETHYL-5-TRIFLUOROMETHYL-1H-BENZIMIDAZOL-1-
YL) PHENETHYL(4-METHYLPHENYL) SULFONYLCARBAMATE

20 METHANESULFONATE

The title compound was prepared according to the procedure described
in Example 221 from 4-(6-chloro-2-ethyl-5-trifluoromethyl-1H-benzimidazol-1-yl) phenethyl(4-methylphenyl) sulfonylcarbamate (Example 106).

m.p.: 172.2 °C.

¹H-NMR (CDCl₃) δ: 9.03 (1H, br.s), 8.52 (1H, s), 7.81 (2H, d, J=8.2 Hz), 7.56
25 (2H, d, J=8.2 Hz), 7.40 (2H, d, J=8.1 Hz), 7.39 (1H, s), 7.29 (2H, d, J=8.1 Hz),

4.35 (2H, t, J=6.3 Hz), 3.16 (2H, q, J=7.6 Hz), 3.06 (2H, t, J=6.3 Hz), 2.94 (3H, s), 2.41 (3H,s), 1.45 (3H, t, J=7.6 Hz).

EXAMPLE 224

5-ACETYL-2-ETHYL-3-(4-{2-[(4-

- 5 METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL
BENZIMIDAZOLE *P*-TOLUENESULFONATE

A mixture of 5-acetyl-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)benzimidazole (Example 78, 43 mg, 0.085 mmol), *p*-toluenesulfonic acid (16.2 mg, 0.085 mmol) in ethanol (0.1 ml) was stirred at room temperature for 16 h. The precipitated crystalline solids were filtered, washed with ethanol (0.05 ml x5), and dried in vacuo at 40 °C for 2 h to afford 54 mg (91%) of the title compound as white solids.

- 15 ¹H-NMR (CDCl₃) δ: 9.85 (1H, br.s), 8.50 (1H, s), 8.02 (1H, d, J=8.9 Hz), 7.86 (2H, d, J=8.1 Hz), 7.68 (2H, dd, J=1.8, 8.2 Hz), 7.47 (2H, d, J=8.4 Hz), 7.36-7.31 (3H, m), 7.22 (2H, d, J=8.4 Hz), 7.17 (2H, d, J=8.4 Hz), 7.00 (1H, br.s), 3.47-3.39 (2H, m) 3.14 (2H, q, J=7.3 Hz), 2.88 (2H, t, J=6.3 Hz), 2.58 (3H, s), 2.35 (3H,s), 2.34 (3H,s), 1.45 (3H, t, J=7.6 Hz).

20 EXAMPLE 225

5-ACETYL-2-ETHYL-3-(4-{2-[(4-

METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)BENZIMIDAZOLE BENZENESULFONATE

- The title compound was prepared according to the procedure described in Example 224 from 5-acetyl-2-ethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)benzimidazole (Example78).

m.p.: 117.7 °C.

¹H-NMR (CDCl₃) δ: 9.62 (1H, br.s), 8.52 (1H, s), 8.05-7.96 (3H, m), 7.67 (2H, d, J=8.2 Hz), 7.49-7.43 (5H, m), 7.37-7.32 (3H, m), 7.19 (2H, d, J=8.2 Hz), 6.92-6.88 (1H, m), 3.48-3.42 (2H, m) 3.17 (2H, q, J=7.6 Hz), 2.89 (2H, t, J=6.1 Hz), 2.61 (3H, s), 2.35 (3H, s), 1.49 (3H, t, J=7.6 Hz).

EXAMPLE 226

4-CHLORO-2-ETHYL-6-METHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-IMIDAZO[4,5-c]PYRIDINE

STEP 1. tert-butyl 2-{4-[(2-chloro-6-methyl-3-nitro-4-pyridinyl)amino]phenyl}ethylcarbamate

A mixture of 2,4-dichloro-6-methyl-3-nitro-pyridine (Chorvat, Robert J. et al., *J.Med.Chem.*, 1999, 42, 833., 7.5 g, 36.2 mmol), [2-(4-amino-phenyl)-ethyl]-carbamic acid tert-butyl ester (Stark, Peter A. et al., *J.Med.Chem.*, 1992, 35, 4264., 1.14 g, 4.83 mmol) in *N,N*-diisopropylethylamine (50 ml) was heated at reflux temperature for 16 h. After cooling, the mixture was concentrated. The residue was diluted with dichloromethane (200 ml) and washed with saturated aqueous NaHCO₃ solution (50 ml x 2). The organic layer was dried (MgSO₄), and concentrated. Purification by flash column chromatography eluting with hexane/ethyl acetate (1:1) to afford 310 mg (16%) of the title compound as orange solids.

¹H-NMR (CDCl₃) δ: 8.19 (1H, s), 7.28 (2H, d, J=8.4 Hz), 7.16 (2H, d, J=8.3 Hz), 6.69 (1H, s), 4.62 (1H, br s), 3.43-3.37 (2H, m), 2.84 (2H, t, J=7.0 Hz), 2.37 (3H, s), 1.44 (9H, s).

STEP 2. tert-butyl 2-{4-[(3-amino-2-chloro-6-methyl-4-pyridinyl)amino]phenyl}ethylcarbamate

The title compound was prepared according to the procedure described in step 1 of Example 6 from *tert*-butyl 2-{4-[(2-chloro-6-methyl-3-nitro-4-pyridinyl)amino]phenyl}ethylcarbamate (step 1).

¹H-NMR (CDCl₃) δ: 7.18 (2H, d, J=8.3 Hz), 7.03 (2H, d, J=8.2 Hz), 6.76 (1H, s), 6.02 (1H, br. s), 4.61 (1H, br. s), 3.40-3.37 (4H, m), 2.78 (2H, t, J=7.0 Hz), 2.33 (3H, s), 1.44 (9H, s).

STEP 3. *tert*-butyl 2-[4-(4-chloro-2-ethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethylcarbamate

A mixture of *tert*-butyl 2-{4-[(3-amino-2-chloro-6-methyl-4-pyridinyl)amino]phenyl}ethylcarbamate (step 2, 238 mg, 0.63 mmol), propionyl chloride (70 mg, 0.76 mmol) in toluene (4.6 ml) and dichloromethane (0.6 ml) was heated at reflux temperature for 1 h. After cooling, the mixture was diluted with ethyl acetate (100 ml) and washed with 1N aqueous NaOH solution (30 ml x 2) and brine (30 ml). The organic layer was dried (MgSO₄), and concentrated.

The residue and *p*-toluenesulfonic acid monohydrate (5 mg, 0.026 mmol) in toluene (5.0 ml) was heated at reflux temperature for 16 h. After cooling, the mixture was diluted with dichloromethane (100 ml) and washed with saturated aqueous NaHCO₃ solution (30 ml) and brine (30 ml). The organic layer was dried (MgSO₄), and concentrated. Purification by PTLC eluting with hexane/ethyl acetate (1:1) to afford 90 mg (34%) of the title compound as a brown oil.

¹H-NMR (CDCl₃) δ: 7.44 (2H, d, J=8.2 Hz), 7.27 (2H, d, J=8.2 Hz), 6.81 (1H, s), 4.75 (1H, br s), 3.52-3.44 (2H, m), 2.94 (2H, t, J=7.1 Hz), 2.82 (2H, q, J=7.6 Hz), 2.55 (3H, s), 1.46 (9H, s), 1.32 (3H, t, J=7.6 Hz).

STEP 4. 2-[4-(4-chloro-2-ethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethanamine

To a stirred solution of *tert*-butyl 2-[4-(4-chloro-2-ethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethylcarbamate (step 3, 90 mg, 0.22 mmol) in dichloromethane (8.5 ml) was added trifluoroacetic acid (1.0 ml, 13.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min, then at room temperature for 5 h. The mixture was concentrated, and diluted with dichloromethane (50 ml), washed with saturated aqueous NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried (MgSO₄), and concentrated. Purification by PTLC eluting with ethyl acetate to afford 50 mg (73%) of the title compound as a brown oil.

¹H-NMR (CDCl₃) δ: 7.45 (2H, d, J=8.2 Hz), 7.27 (2H, d, J=8.2 Hz), 6.81 (1H, s), 3.09 (2H, t, J=6.9 Hz), 2.89 (2H, t, J=6.8 Hz), 2.83 (2H, q, J=7.4 Hz), 2.55 (3H, s), 1.31 (3H, t, J=7.4 Hz).

STEP 5. 4-chloro-2-ethyl-6-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-imidazo[4,5-*c*]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(4-chloro-2-ethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethanamine (step 4).

m.p.: 163°C.

MS (ESI) *m/z*: 512 [(MH)⁺], 510 [(M-H)⁻].

¹H-NMR (CDCl₃) δ: 7.73 (2H, d, J=8.2 Hz), 7.38-7.21 (6H, m), 6.78 (1H, s), 3.53-3.51 (2H, m), 2.91-2.89 (2H, m), 2.79 (2H, q, J=7.2 Hz), 2.52 (3H, s), 2.37 (3H, s), 1.29 (3H, t, J=7.2 Hz).

EXAMPLE 227

2-[4-(2-ETHYL-4,6-DIMETHYL-1*H*-IMIDAZO[4,5-*c*]PYRIDIN-1-
YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-ethyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethanol (step 4 of Example 42).

m.p.: 158°C.

- 5 MS (ESI) *m/z*: 493 [(MH)⁺], 491 [(M-H)⁺].

¹H-NMR (DMSO-*d*₆) δ: 7.72 (2H, d, *J*=8.2 Hz), 7.47 (2H, d, *J*=8.6 Hz), 7.43 (2H, d, *J*=8.6 Hz), 7.34 (2H, d, *J*=8.0 Hz), 6.96 (1H, s), 4.18 (2H, t, *J*=6.6 Hz), 2.94 (2H, t, *J*=6.4 Hz), 2.76 (3H, s), 2.74 (2H, q, *J*=7.3 Hz), 2.50 (3H, s), 2.35 (3H, s), 1.23 (3H, t, *J*=7.3 Hz).

10 EXAMPLE 228

2-[4-(8-ETHYL-2,6-DIMETHYL-9*H*-PURIN-9-*YL*)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[(6-chloro-2-methyl-5-nitro-4-pyrimidinyl)amino]phenyl}ethanol

- 15 To a stirred solution of 4,6-dichloro-2-methyl-5-nitro-pyrimidine (Albert et al., *J.Chem.Soc.*, 1954, 3832, 7.5 g, 36.1 mmol) in THF (150 ml) was added 4-aminophenylethyl alcohol (2.47 g, 18.0 mmol), triethylamine (3.65 g, 36.1 mmol), and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water (10ml), and the mixture was extracted with ethyl acetate (100 ml x 3). The organic layer was washed with brine (50 ml), dried (MgSO₄), and concentrated. Purification by flash column chromatography eluting with hexane/ethyl acetate (gradient elution from 1:1 to 1:2) to afford 4.0 g (72%) of the title compound as a yellow solid.
- 20

¹H-NMR (CDCl₃) δ: 9.34 (1H, s), 7.50 (2H, d, *J*=8.4 Hz), 7.28 (2H, d, *J*=8.8 Hz), 3.89 (2H, t, *J*=6.6 Hz), 2.90 (2H, t, *J*=6.4 Hz), 2.57 (3H, s).

- 25 STEP 2. diethyl 2-(6-{[4-(2-Hydroxyethyl)phenyl]amino}-2-methyl-5-nitro-4-pyrimidinyl)propanedioate

To a stirred solution of 2-{4-[(6-chloro-2-methyl-5-nitro-4-pyrimidinyl)amino]phenyl} ethanol (step 1, 2.0 g, 6.48 mmol) in acetone (61 ml) was added diethyl malonate (1.53 g, 9.54 mmol) at 0 °C, then aqueous NaOH solution (11N, 2 ml, 22 mmol) was added dropwise over 20 min. After addition, the mixture was stirred at room temperature for 1 h. The reaction was quenched with water (120 ml), and the pH value was adjusted to 8.0 by addition of acetic acid. The whole was extracted with ethyl acetate (100 ml x 3). The organic layer was washed with brine (50 ml), dried (MgSO₄), and concentrated.

Removal of excess diethyl malonate by azeotropic distillation with toluene

afforded 3.26 g (72%) of the title compound as a brown oil.

MS (EI) m/z: 432 (M⁺).

¹H-NMR (CDCl₃) δ: 10.15 (1H, s), 7.55 (2H, d, J=8.4 Hz), 7.27 (2H, d, J=8.4 Hz), 5.36 (1H, s), 4.31 (4H, q, J=7.1 Hz), 3.90 (2H, t, J=6.6 Hz), 2.90 (2H, t, J=6.4 Hz), 2.56 (3H, s), 1.32 (6H, t, J=7.1 Hz).

STEP 3. 2-{4-[(2,6-dimethyl-5-nitro-4-pyrimidinyl)amino]phenyl} ethanol

A mixture of diethyl 2-(6-{[4-(2-hydroxyethyl)phenyl]amino}-2-methyl-5-nitro-4-pyrimidinyl)propanedioate (step 2, 2.0 g, 6.48 mmol) in 2N aqueous HCl (15 ml) was heated at reflux temperature for 5 h. After cooling, the reaction was quenched with saturated NaHCO₃ aqueous solution (100 ml), and the whole was extracted with ethyl acetate (100 ml x 3). The organic layer was washed with brine (50 ml), dried (MgSO₄), and concentrated. Purification by flash column chromatography eluting with hexane/ethyl acetate (gradient elution from 1:1 to 0:100) to afford 1.33 g (71%) of the title compound as a yellow solid.

MS (EI) m/z: 288 (M⁺).

¹H-NMR (CDCl₃) δ: 9.81 (1H, s), 7.56 (2H, d, J=8.4 Hz), 7.27 (2H, d, J=8.4 Hz), 3.92-3.86 (2H, m), 2.89 (2H, t, J=6.4 Hz), 2.76 (3H, s), 2.56 (3H, s).

STEP 4. 2-{4-[(5-amino-2,6-dimethyl-4-pyrimidinyl)amino]phenyl} ethanol

The title compound was prepared according to the procedure described in step 1 of Example 6 from 2-{4-[(2,6-dimethyl-5-nitro-4-pyrimidinyl)amino]phenyl}ethanol (step 3).

MS (EI) m/z : 258 (M^+).

- 5 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 8.14 (1H, s), 7.63 (2H, d, $J=8.6$ Hz), 7.12 (2H, d, $J=8.4$ Hz), 4.67 (2H, br.s), 3.58 (2H, t, $J=7.3$ Hz), 2.67 (2H, t, $J=7.2$ Hz), 2.28 (3H, s), 2.20 (3H, s).

STEP 5. 2-[4-(8-ethyl-2,6-dimethyl-9H-purin-9-yl)phenyl]ethyl propanoate

- 10 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(5-amino-2,6-dimethyl-4-pyrimidinyl)amino]phenyl}ethanol (step 4).

$^1\text{H-NMR}$ (CDCl_3) δ : 7.44 (2H, d, $J=8.2$ Hz), 7.31 (2H, d, $J=8.2$ Hz), 4.37 (2H, t, $J=6.9$ Hz), 3.06 (2H, t, $J=6.8$ Hz), 2.84 (3H, s), 2.82 (2H, q, $J=7.4$ Hz), 2.70 (3H, s), 2.35 (2H, q, $J=7.6$ Hz), 1.31 (3H, t, $J=7.6$ Hz), 1.15 (3H, t, $J=7.6$ Hz).

- 15 STEP 6. 2-[4-(8-ethyl-2,6-dimethyl-9H-purin-9-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(8-ethyl-2,6-dimethyl-9H-purin-9-yl)phenyl]ethyl propanoate (step 5).

- 20 $^1\text{H-NMR}$ (CDCl_3) δ : 7.46 (2H, d, $J=8.4$ Hz), 7.31 (2H, d, $J=8.3$ Hz), 3.99-3.92 (2H, m), 2.99 (2H, t, $J=6.4$ Hz), 2.85 (3H, s), 2.83 (2H, q, $J=7.5$ Hz), 2.70 (3H, s), 1.32 (3H, t, $J=7.3$ Hz).

STEP 7. 2-[4-(8-ethyl-2,6-dimethyl-9H-purin-9-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate

- 25 The title compound was prepared according to the procedure described in Example 3 from 2-[4-(8-ethyl-2,6-dimethyl-9H-purin-9-yl)phenyl]ethanol (step 6).

m.p.: 162°C.

MS (ESI) m/z: 494 [(MH)⁺], 492 [(M-H)].

¹H-NMR (CDCl₃) δ: 7.94 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.1 Hz), 7.24 (2H, d, J=8.6 Hz), 7.18 (2H, d J=8.4 Hz), 4.36 (2H, t, J=6.4 Hz), 2.97 (2H, t, J=6.2 Hz), 2.86 (3H, s), 2.79 (2H, q, J=7.6 Hz), 2.64 (3H, s), 2.44 (3H, s), 1.28 (3H, t, J=7.6 Hz).

EXAMPLE 229

2-[4-(4,6-DIMETHYL-2-PHENYL-1H-IMIDAZO[4,5-c]PYRIDIN-1-

YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-[4-(4,6-dimethyl-2-phenyl-1H-imidazo[4,5-c]pyridin-1-

yl)phenyl]ethyl benzoate

A mixture of 2-{4-[(3-Amino-2,6-dimethyl-4-pyridinyl)amino]phenyl}ethanol (step 2 of Example 42, 500 mg, 1.94 mmol), benzoic acid (4.45 g 36.4 mmol), benzoic anhydride (4.8 g, 21.2 mmol) was heated at 120 °C for 4 h. After cooling, the mixture was diluted with dichloromethane (100 ml). The solution was washed with saturated NaHCO₃ aqueous solution (50 ml), brine (50 ml), dried (MgSO₄), and concentrated. Purification by flash column chromatography eluting with ethyl acetate to afford 813 mg (94%) of the title compound as a white solid.

MS (EI) m/z: 447(M⁺).

¹H-NMR (CDCl₃) δ: 8.02-7.21 (14H, m), 6.87 (1H, s), 4.61 (2H, t, J=7.0 Hz), 3.18 (2H, t, J=6.8 Hz), 2.96 (3H, s), 2.61 (3H, s).

STEP 2. 2-[4-(4,6-dimethyl-2-phenyl-1H-imidazo[4,5-c]pyridin-1-

yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(4,6-dimethyl-2-phenyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl benzoate (step 1).

¹H-NMR (CDCl₃) δ: 7.57-7.18 (9H, m), 6.87 (1H, s), 3.95 (2H, t, J=6.6 Hz), 2.96 (2H, t, J=6.6 Hz), 2.94 (3H, s), 2.59 (3H, s).

STEP 3. 2-[4-(4,6-dimethyl-2-phenyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(4,6-dimethyl-2-phenyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethanol (step 2).

m.p.: 194°C.

MS (ESI) m/z: 541 [(MH)⁺], 539 [(M-H)⁻].

¹H-NMR (CDCl₃) δ: 7.89 (2H, d, J=8.2 Hz), 7.46-6.95 (11H, m), 6.77 (1H, s), 4.35 (2H, t, J=6.0 Hz), 3.03 (3H, s), 2.96 (2H, t, J=6.0 Hz), 2.56 (3H, s), 2.42 (3H, s).

EXAMPLE 230

2-[4-(2-BUTYL-4,6-DIMETHYL-1*H*-IMIDAZO[4,5-*c*]PYRIDIN-1-YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl pentanoate

The title compound was prepared according to the procedure described in step 1 of Example 229 from 2-[4-[(3-Amino-2,6-dimethyl-4-pyridinyl)amino]phenyl]ethanol (step 2 of Example 42).

¹H-NMR (CDCl₃) δ: 7.44 (2H, d, J=8.1 Hz), 7.26 (2H, d, J=8.2 Hz), 6.71 (1H, s), 4.38 (2H, t, J=6.9 Hz), 3.07 (2H, t, J=6.9 Hz), 2.88 (3H, s), 2.78 (2H, t, J=7.6 Hz), 2.56 (3H, s), 2.33 (2H, t, J=7.4 Hz), 1.74-1.55 (4H, m), 1.41-1.24 (4H, m), 0.91 (3H, t, J=7.2 Hz), 0.84 (3H, t, J=7.2 Hz).

STEP 2. 2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl pentanoate (step 1).

¹H-NMR (CDCl₃) δ: 7.46 (2H, d, J=8.2 Hz), 7.25 (2H, d, J=8.2 Hz), 6.72 (1H, s), 4.00 (2H, t, J=6.6 Hz), 3.02 (2H, t, J=6.4 Hz), 2.88 (3H, s), 2.78 (2H, t, J=7.6 Hz), 2.54 (3H, s), 1.76-1.64 (2H, m), 1.39-1.25 (2H, m), 0.85 (3H, t, J=7.4 Hz).

STEP 3. 2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethanol (step 2).

m.p.: 162°C.

MS (ESI) *m/z*: 521 [(MH)⁺], 519 [(M-H)⁻].

¹H-NMR (CD₃OD) δ: 7.97 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=7.9 Hz), 7.18 (2H, d, J=8.4 Hz), 6.84 (2H, d, J=8.4 Hz), 6.60 (1H, s), 4.34 (2H, t, J=5.5 Hz), 3.03 (3H, s), 2.96 (2H, t, J=5.5 Hz), 2.71 (2H, t, J=7.5 Hz), 2.52 (3H, s), 2.43 (3H, s), 1.72-1.62 (2H, m), 1.36-1.24 (2H, m), 0.84 (3H, t, J=7.3 Hz).

EXAMPLE 231

2-[4-(2-BUTYL-4,6-DIMETHYL-1*H*-IMIDAZO[4,5-*c*]PYRIDIN-1-YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE *P*-TOLUENESULFONATE

To a solution of 2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate (Example 230) in methanol was added TsOH (1.0 eq.). The resulting mixture was stirred at room temperature for 5 min and concentrated. The residual solids were collected and dried under reduced pressure at 50 °C to afford the title compound as white solids:

¹H-NMR (CDCl₃) δ: 7.89-7.86 (4H, m), 7.49 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.1 Hz), 7.24 (2H, d, J=8.3 Hz), 7.18 (2H, d, J=7.9 Hz), 7.03 (1H, s), 4.34 (2H, t, J=6.2 Hz), 3.12 (3H, s), 3.02 (2H, t, J=6.2 Hz), 2.80 (3H, s), 2.77 (2H, t, J=8.1 Hz), 2.42 (3H, s), 2.34 (3H, s), 1.78-1.68 (2H, m), 1.39-1.27 (2H, m), 0.86 (3H, t, J=7.3 Hz).

EXAMPLE 232

2-[4-(4,6-DIMETHYL-2-(1-METHYLETHYL)-1H-IMIDAZO[4,5-c]PYRIDIN-1-YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[4,6-dimethyl-2-(1-methylethyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethyl 2-methylpropanoate

The title compound was prepared according to the procedure described in step 1 of Example 229 from 2-{4-[(3-Amino-2,6-dimethyl-4-pyridinyl)amino]phenyl}ethanol (step 2 of Example 42).

¹H-NMR (CDCl₃) δ: 7.44 (2H, d, J=8.4 Hz), 7.26 (2H, d, J=8.4 Hz), 6.66 (1H, s), 4.38 (2H, t, J=7.0 Hz), 3.08 (2H, t, J=6.8 Hz), 3.12-3.02 (1H, m), 2.89 (3H, s), 2.55 (3H, s), 2.61-2.48 (1H, m), 1.33 (6H, d, J=7.0 Hz), 1.15 (6H, d, J=7.0 Hz).

STEP 2. 2-{4-[4,6-dimethyl-2-(1-methylethyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[4,6-dimethyl-2-(1-methylethyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethyl 2-methylpropanoate (step 1).

¹H-NMR (CDCl₃) δ: 7.46 (2H, d, J=8.2 Hz), 7.25 (2H, d, J=8.3 Hz), 6.68 (1H, s), 4.00 (2H, t, J=6.6 Hz), 3.13-3.04 (1H, m), 3.02 (2H, t, J=6.6 Hz), 2.88 (3H, s), 2.53 (3H, s), 1.33 (6H, d, J=7.0 Hz).

STEP 3. 2-{4-[4,6-dimethyl-2-(1-methylethyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[4,6-dimethyl-2-(1-methylethyl)-1H-imidazo[4,5-

5 c]pyridin-1-yl]phenyl}ethanol (step 2).

m.p.: 213°C.

MS (ESI) m/z: 507 [(MH)⁺], 505 [(M-H)⁻].

¹H-NMR (CD₃OD) δ: 7.80 (2H, d, J=8.4 Hz), 7.51 (2H, d, J=8.6 Hz), 7.34 (2H, d, J=8.6 Hz), 7.29 (2H, d, J=8.1 Hz), 7.01 (1H, s), 4.26 (2H, t, J=6.6 Hz), 3.15-3.09 (1H, m), 3.00 (2H, t, J=6.4 Hz), 2.90 (3H, s), 2.58 (3H, s), 2.36 (3H, s), 1.33 (6H, d, J=6.8 Hz).

EXAMPLE 233

2-{4-[2-(1,1-DIMETHYLETHYL)-4,6-DIMETHYL-1H-IMIDAZO[4,5-c]PYRIDIN-1-YL]PHENYL}ETHYL (4-

METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[2-(1,1-dimethylethyl)-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethyl 2,2-dimethylpropanoate

The title compound was prepared according to the procedure described in step 1 of Example 229 from 2-{4-[(3-Amino-2,6-dimethyl-4-pyridinyl)amino]phenyl}ethanol (step 2 of Example 42).

¹H-NMR (CDCl₃) δ: 7.41 (2H, d, J=8.4 Hz), 7.26 (2H, d, J=8.4 Hz), 6.35 (1H, s), 4.38 (2H, t, J=6.6 Hz), 3.08 (2H, t, J=6.6 Hz), 2.87 (3H, s), 2.50 (3H, s), 1.34 (9H, s), 1.17 (9H, s).

STEP 2. 2-{4-[2-(1,1-dimethylethyl)-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[2-(1,1-dimethylethyl)-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]phenyl}ethyl 2,2-dimethylpropanoate (step 1).

¹H-NMR (CDCl₃) δ: 7.42 (2H, d, J=8.1 Hz), 7.27 (2H, d, J=8.6 Hz), 6.38 (1H, s), 4.00 (2H, t, J=6.4 Hz), 3.01 (2H, t, J=6.6 Hz), 2.87 (3H, s), 2.50 (3H, s), 1.34 (9H, s).

STEP 3. 2-{4-[2-(1,1-dimethylethyl)-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[2-(1,1-dimethylethyl)-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]phenyl}ethanol (step 2).

m.p.: 226°C.

MS (ESI) *m/z*: 521 [(MH)⁺], 519 [(M-H)⁻].

¹H-NMR (DMSO-*d*₆) δ: 7.71 (2H, d, J=8.3 Hz), 7.46 (2H, d, J=8.6 Hz), 7.41 (2H, d, J=8.6 Hz), 7.35 (2H, d, J=8.1 Hz), 6.55 (1H, s), 4.20 (2H, t, J=7.0 Hz), 2.95 (2H, t, J=7.0 Hz), 2.74 (3H, s), 2.44 (3H, s), 2.36 (3H, s), 1.27 (9H, s).

EXAMPLE 234

2-[4-(2-CYCLOHEXYL-4,6-DIMETHYL-1*H*-IMIDAZO[4,5-*c*]PYRIDIN-1-YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-[4-(2-cyclohexyl)-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]phenyl]ethyl cyclohexanecarboxylate

The title compound was prepared according to the procedure described in step 1 of Example 229 from 2-{4-[(3-Amino-2,6-dimethyl-4-pyridinyl)amino]phenyl}ethanol (step 2 of Example 42).

¹H-NMR (CDCl₃) δ: 7.44 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 6.65 (1H, s), 4.39 (2H, t, J=6.8 Hz), 3.08 (2H, t, J=6.8 Hz), 2.88 (3H, s), 2.54 (3H, s), 2.71-1.21 (22H, m).

STEP 2. 2-[4-(2-cyclohexyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(2-cyclohexyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl cyclohexanecarboxylate (step 1).

¹H-NMR (CDCl₃) δ: 7.46 (2H, d, J=8.2 Hz), 7.25 (2H, d, J=8.2 Hz), 6.68 (1H, s), 4.01 (2H, t, J=6.4 Hz), 3.02 (2H, t, J=6.4 Hz), 2.88 (3H, s), 2.72-2.70 (1H, m), 2.54 (3H, s), 2.30-1.15 (10H, m).

STEP 3. 2-[4-(2-cyclohexyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-cyclohexyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethanol (step 2).

m.p.: 168°C.

MS (ESI) m/z: 547 [(MH)⁺], 545 [(M-H)⁻].

¹H-NMR (CD₃OD) δ: 7.97 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.1 Hz), 7.19 (2H, d, J=8.3 Hz), 6.77 (2H, d, J=8.2 Hz), 6.53 (1H, s), 4.33 (2H, t, J=5.3 Hz), 3.09 (3H, s), 2.97 (2H, t, J=5.5 Hz), 2.65-2.55 (1H, m), 2.50 (3H, s), 2.42 (3H, s), 1.77-1.18 (10H, m).

EXAMPLE 235

2-{4-[4,6-DIMETHYL-2-(3-PHENYLPROPYL)-1*H*-IMIDAZO[4,5-*c*]PYRIDIN-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-[4-[4,6-dimethyl-2-(3-phenylpropyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]phenyl]ethyl 4-phenylbutanoate

The title compound was prepared according to the procedure described in step 1 of Example 229 from 2-[4-[(3-Amino-2,6-dimethyl-4-pyridinyl)amino]phenyl]ethanol (step 2 of Example 42).

¹H-NMR (CDCl₃) δ: 7.39 (2H, d, J=8.2 Hz), 7.30-7.15 (10H, m), 7.06 (2H, d, J=6.4 Hz), 6.70 (1H, s), 4.37 (2H, t, J=7.1 Hz), 3.06 (2H, t, J=6.9 Hz), 2.88 (3H, s), 2.80 (2H, t, J=7.6 Hz), 2.68-2.60 (4H, m), 2.54 (3H, s), 2.36 (2H, t, J=7.4 Hz), 2.09-1.91 (4H, m).

5 STEP 2. 2-{4-[4,6-dimethyl-2-(3-phenylpropyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[4,6-dimethyl-2-(3-phenylpropyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethyl 4-phenylbutanoate (step 1).

10 ¹H-NMR (CDCl₃) δ: 7.41 (2H, d, J=8.2 Hz), 7.25-7.15 (5H, m), 7.07 (2H, d, J=6.8 Hz), 6.72 (1H, s), 3.99 (2H, t, J=6.6 Hz), 3.00 (2H, t, J=6.3 Hz), 2.88 (3H, s), 2.81 (2H, t, J=7.6 Hz), 2.64 (2H, d, J=7.6 Hz), 2.55 (3H, s), 2.11-2.00 (2H, m).

15 STEP 3. 2-{4-[4,6-dimethyl-2-(3-phenylpropyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[4,6-dimethyl-2-(3-phenylpropyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethanol (step 2).
m.p.: 175°C.

20 MS (ESI) m/z: 583 [(MH)⁺], 581 [(M-H)⁻].

¹H-NMR (CDCl₃) δ: 7.95 (2H, d, J=8.3 Hz), 7.30-7.14 (7H, m), 7.03 (2H, d, J=8.1 Hz), 6.81 (2H, d, J=8.0 Hz), 6.64 (1H, s), 4.33 (2H, t, J=5.7 Hz), 3.00 (3H, s), 2.95 (2H, t, J=5.7 Hz), 2.72 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.4 Hz), 2.51 (3H, s), 2.41 (3H, s), 2.07-1.97 (2H, m).

25 EXAMPLE 236

4-METHYL-N-[(2-{4-[5-(METHYLOXY)-2-(1H-PYRAZOL-3-YL)-1H-BENZIMIDAZOL-1-

YL[PHENYL]ETHYL)AMINO]CARBONYL}BENZENESULFONAMIDE *P*-
TOLUENESULFONATE

STEP 1. 2-{4-[5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-
yl]phenyl}ethanol

- 5 A mixture of 2-(4-{[2-amino-4-(methyloxy)phenyl]amino}phenyl)ethanol (step 2 of Example 71, 1.95 g, 7.56 mmol), pyrazol-3-carbaldehyde (726 mg, 7.56 mmol) in ethanol (45 ml) was heated at reflux temperature for 2 h. After cooling, the mixture was concentrated. A mixture of the residue, lead tetraacetate (4.61 g, 8.32 mmol) in
- 10 benzene (50 ml) was stirred at room temperature for 16 h. The mixture was quenched with saturated NaHCO₃ aqueous solution (150 ml). The whole was extracted with ethyl acetate (150 ml x 4). The organic layer was washed with water (100 ml x 5), brine (50 ml), dried (MgSO₄), and concentrated. Purification by flash column chromatography eluting with dichloromethane/methanol
- 15 (gradient elution from 20:1 to 10:1) to afford 408 mg (16%) of the title compound as an amber solid.

MS (EI) *m/z*: 334 (M⁺).

- ¹H-NMR (DMSO-*d*₆) δ: 7.6 (1H, br.s), 7.43 (2H, d, *J*=7.7 Hz), 7.29-7.23 (3H,m), 7.04 (1H, d, *J*=8.8 Hz), 6.90 (1H, d, *J*=8.8 Hz), 6.34 (1H, br.s), 3.85-3.81 (5H, m), 2.92 (2H, t, *J*=6.6 Hz).
- 20

STEP 2. 1-[4-(2-chloroethyl)phenyl]-5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-
benzimidazole

- The title compound was prepared according to the procedure described in step 7 Example 1 from 2-{4-[5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-
- 25 benzimidazol-1-yl]phenyl}ethanol (step 1).

MS (EI) *m/z*: 352 (M⁺).

¹H-NMR (CDCl₃) δ: 8.96 (0.5H, s), 8.11 (0.5H, d, J=2.9 Hz), 7.50 (0.5H, d, J=2.0 Hz), 7.46-7.34 (5H, m), 7.05 (1H, dd, J=16.5, 8.8 Hz), 6.93 (1H, ddd, J=1.4, 9.0, 2.4 Hz), 6.71 (0.5H, dd, J=2.9, 1.1 Hz), 5.81 (1H, s), 3.85 (3H, s), 3.82 (2H, t, J=7.0 Hz), 3.22 (2H, t, J=7.0 Hz).

5 STEP 3. 1-[4-(2-azidoethyl)phenyl]-5-(methyloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 8 Example 1 from 1-[4-(2-chloroethyl)phenyl]-5-(methyloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole (step 2).

10 MS (EI) m/z: 359 (M⁺).

¹H-NMR (CDCl₃) δ: 14.05 (1H, br.s), 7.53-7.50 (2H, m), 7.45 (2H, d, J=8.4 Hz), 7.37 (2H, d, J=8.4 Hz), 7.01 (1H, d, J=8.7 Hz), 6.89 (1H, dd, J=8.7, 2.4 Hz), 5.81 (1H, s), 3.85 (3H, s), 3.61 (2H, t, J=6.9 Hz), 3.03 (2H, t, J=6.9 Hz).

15 STEP 4. 2-{4-[5-(methyloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazol-1-yl]phenyl}ethylamine

The title compound was prepared according to the procedure described in step 9 Example 1 from 1-[4-(2-azidoethyl)phenyl]-5-(methyloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole (step 3).

MS (EI) m/z: 333 (M⁺).

20 ¹H-NMR (CDCl₃) δ: 7.47 (1H, d, J=2.0 Hz), 7.43-7.29 (5H, m), 7.00 (1H, d, J=8.8 Hz), 6.88 (1H, dd, J=9.0, 2.4 Hz), 5.81 (1H, s), 3.80 (3H, s), 3.09 (2H, t, J=7.1 Hz), 2.90 (2H, t, J=6.8 Hz).

25 STEP 5. 4-methyl-N-{[(2-{4-[5-(methyloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}benzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-{4-[5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-yl]phenyl}ethylamine (step 4).

MS (ESI) *m/z*: 531 [(MH)⁺], 529 [(M-H)⁻].

- 5 ¹H-NMR (CDCl₃) δ: 7.77 (2H, d, J=8.3 Hz), 7.44 (1H, s), 7.24 (2H, d, J=7.5 Hz), 7.14-7.07 (5H, m), 6.98 (1H, d, J=9.0 Hz), 6.88 (1H, d, J=9.0 Hz), 6.10 (1H, s), 3.83 (3H, s), 3.57-3.55 (2H, m), 2.88-2.84 (2H, m), 2.35 (3H, s).

- 10 STEP 6. 4-methyl-*N*-{[(2-{4-[5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}benzenesulfonamide *p*-toluenesulfonamide mono-*p*-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from 4-methyl-*N*-{[(2-{4-[5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}benzenesulfonamide (step 5).

- 15 ¹H-NMR (CDCl₃) δ: 12.65 (1H, s), 9.99 (1H, s), 7.87 (2H, d, J=8.1 Hz), 7.78 (2H, d, J=8.3 Hz), 7.50 (2H, d, J=9.0 Hz), 7.39 (2H, d, J=8.4 Hz), 7.20 (2H, d, J=7.9 Hz), 7.18 (2H, d, J=8.1 Hz), 7.08-6.93 (5H, m), 6.44 (1H, s), 3.76 (3H, s), 3.42-3.40 (2H, m), 2.92-2.88 (2H, m), 2.86 (6H, s).

20

EXAMPLE 237

2-{4-[5-METHYLOXY-2-(1*H*-PYRAZOL-3-YL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE *P*-TOLUENESULFONATE

- 25 STEP 1. 2-{4-[5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-yl]phenyl}ethanol (step 1 of Example 236).

MS (ESI) *m/z*: 532 [(MH)⁺], 530 [(M-H)⁻].

- 5 ¹H-NMR (DMSO-*d*₆) δ: 7.75 (2H, d, *J*=8.1 Hz), 7.58 (2H, d, *J*=8.1 Hz), 7.38 (2H, d, *J*=7.8 Hz), 7.33-7.21 (3H, m), 7.22 (2H, d, *J*=8.1 Hz), 6.96 (1H, d, *J*=8.1 Hz), 6.88 (1H, d, *J*=8.1 Hz), 4.26-4.24 (2H, m), 3.82 (3H, s), 2.95-2.93 (2H, m), 2.34 (3H, s).

10 STEP 2. 2-{4-[5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate mono-*p*-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from 2-{4-[5-(methyloxy)-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (step 1).

- 15 ¹H-NMR (CDCl₃) δ: 7.88 (2H, d, *J*=8.2 Hz), 7.80-7.65 (6H, m), 7.44 (2H, d, *J*=8.1 Hz), 7.38-7.26 (3H, m), 7.17 (2H, d, *J*=8.1 Hz), 7.10 (2H, d, *J*=7.6 Hz), 4.37-4.33 (2H, m), 3.03-2.99 (2H, m), 2.39 (3H, s), 2.35 (3H, s), 2.31 (3H, s).

EXAMPLE 238

- 20 2-{4-[6-CHLORO-2-(1,5-DIMETHYL-1*H*-PYRAZOL-3-YL)-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 2-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl (4-methylphenyl)sulfonylcarbamate

- To a stirred solution of 2-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)ethanol (step 2 of Example 104, 1.0 g, 2.77 mmol) in dichloromethane (45 ml) was added *p*-toluenesulfonyl isocyanate (574 mg, 2.91 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was quenched with water (100 ml). The organic layer was separated. The aqueous layer was extracted with dichloromethane (100 ml x 3).
- 25

The combined organic layer was washed with brine (50 ml), dried (MgSO₄), and concentrated. Purification by flash column chromatography eluting with hexane/ethyl acetate (gradient elution from 2:1 to 1:1) to afford 1.51 g (98%) of the title compound as an orange solid.

¹H-NMR (CDCl₃) δ: 9.68 (1H, s), 8.58 (1H, s), 7.91 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=7.9 Hz), 7.27 (2H, d, J=7.9 Hz), 7.20 (2H, d, J=8.4 Hz), 7.17 (1H, s), 4.33 (2H, t, J=7.0 Hz), 2.96 (2H, t, J=6.8 Hz), 2.45 (3H, s).

STEP 2. 2-(4-{{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

To a stirred solution of 2-(4-{{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (step 1, 1.51 g, 2.71 mmol) in methanol (250 ml) was added 5% platinum-sulfided on carbon (600 mg). The mixture was stirred at room temperature for 5 h under hydrogen atmosphere (4 atm). The palladium catalyst was removed by filtration and washed with dichloromethane (100 ml). The filtrate was concentrated under reduced pressure to afford 1.46 g (99%) of the title compound as a brown oil.

¹H-NMR (CDCl₃) δ: 7.90 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.2 Hz), 7.16 (1H, s), 7.07 (2H, d, J=8.2 Hz), 7.06 (1H, s), 6.86 (2H, d, J=8.2 Hz), 5.40 (2H, s), 4.26 (2H, t, J=6.9 Hz), 2.85 (2H, t, J=7.2 Hz), 2.44 (3H, s).

STEP 3. 2-(4-{{[5-chloro-2-{{(1,5-dimethyl-1H-pyrazol-3-yl)carbonyl]amino}-4-(trifluoromethyl)phenyl]amino}phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

To a stirred solution of 2-(4-{{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (step 2, 200 mg, 0.379 mmol) in dichloromethane (1.7 ml) was added a solution of 1,5-dimethyl-1H-pyrazole-3-carboxylic acid (63.8 mg, 0.455 mmol) and *N,N*-diisopropylethylamine (118 mg, 0.909 mmol) in dichloromethane (1.7 ml), then

to the mixture was added a solution of HOBt (61.5 mg, 0.455 mmol) and HBTU (431 mg, 1.14 mmol) in DMF (2.5 ml), and the mixture was stirred at room temperature for 20 h. The mixture was quenched with water (100 ml). The whole was extracted with ethyl acetate (100 ml x 3). The combined organic layer was washed with water (100 ml x 3), brine (50 ml), dried (MgSO₄), and concentrated. Purification by PTLC eluting with hexane/ethyl acetate (1:1) to afford 145 mg (59%) of the title compound as a red solid.

¹H-NMR (CDCl₃) δ: 8.70 (1H, s), 7.87 (2H, d, J=8.1 Hz), 7.79 (1H, s), 7.28 (2H, d, J=8.1 Hz), 7.04 (2H, d, J=8.3 Hz), 6.95 (2H, d, J=8.3 Hz), 6.72 (1H, s), 6.60 (1H, s), 4.22 (2H, t, J=6.8 Hz), 3.78 (3H, s), 2.84-2.80 (2H, m), 2.40 (3H, s), 2.30 (3H, s).

STEP 4. 2-{4-[6-chloro-2-(1,5-dimethyl-1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

A mixture of 2-(4-{[5-chloro-2-[(1,5-dimethyl-1H-pyrazol-3-yl)carbonyl]amino}-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl (4-methylphenyl)sulfonylcarbamate (step 3, 145 mg, 0.223 mmol) in 2N NaOH (1 ml) and ethanol (2 ml) was stirred at 50 °C for 85 h. After cooling, the pH value was adjusted to 4.0 by addition of 2N HCl. The mixture was diluted with water (80 ml), and extracted with dichloromethane (80 ml x 3). The combined organic layer was washed with brine (50 ml), dried (MgSO₄), and concentrated. Purification by PTLC eluting with hexane/ethyl acetate (1:3) to afford 30 mg (21%) of the title compound as a red solid.

MS (ESI) m/z: 632 [(MH)⁺], 630 [(M-H)⁻].

¹H-NMR (CDCl₃) δ: 8.15 (1H, s), 7.90 (2H, d, J=8.4 Hz), 7.34-7.24 (6H, m), 7.19 (1H, s), 5.81 (1H, s), 4.40 (2H, t, J=6.8 Hz), 3.76 (3H, s), 3.04 (2H, t, J=6.4 Hz), 2.41 (3H, s), 2.20 (3H, s).

EXAMPLE 239

N-[({2-[4-(2-BUTYL-4,6-DIMETHYL-1*H*-IMIDAZO[4,5-*c*]PYRIDIN-1-YL)PHENYL]ETHYL}AMINO)CARBONYL]-4-METHYLBENZENESULFONAMIDE
STEP 1. 2-butyl-1-[4-(2-chloroethyl)phenyl]-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridine

- 5 The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethanol (step 2 of Example 230).

MS (EI) *m/z*: 341 (*M*⁺).

- 10 ¹H-NMR (CDCl₃) δ: 7.45 (2H, d, *J*=8.2 Hz), 7.28 (2H, d, *J*=8.2 Hz), 6.73 (1H, s), 3.82 (2H, t, *J*=7.1 Hz), 3.22 (2H, t, *J*=7.1 Hz), 2.89 (3H, s), 2.79 (2H, t, *J*=8.2 Hz), 2.58 (3H, s), 1.76-1.64 (2H, m), 1.39-1.25 (2H, m), 0.84 (3H, t, *J*=7.2 Hz).

STEP 2. 1-[4-(2-azidoethyl)phenyl]-2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridine

- 15 The title compound was prepared according to the procedure described in step 8 of Example 1 from 2-butyl-1-[4-(2-chloroethyl)phenyl]-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridine (step 1).

MS (EI) *m/z*: 348 (*M*⁺).

- 20 ¹H-NMR (CDCl₃) δ: 7.46 (2H, d, *J*=8.2 Hz), 7.29 (2H, d, *J*=8.6 Hz), 6.72 (1H, s), 3.62 (2H, t, *J*=6.8 Hz), 3.03 (2H, t, *J*=6.8 Hz), 2.88 (3H, s), 2.78 (2H, t, *J*=7.6 Hz), 2.55 (3H, s), 1.74-1.63 (2H, m), 1.38-1.24 (2H, m), 0.84 (3H, t, *J*=7.3 Hz).

STEP 3. 2-[4-(2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenyl]ethylamine

- 25 The title compound was prepared according to the procedure described in step 9 of Example 1 from 1-[4-(2-azidoethyl)phenyl]-2-butyl-4,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridine (step 2).

MS (EI) *m/z*: 322 (*M*⁺).

¹H-NMR (CDCl₃) δ: 7.43 (2H, d, J=8.3 Hz), 7.26 (2H, d, J=8.1 Hz), 6.72 (1H, s), 3.10-3.04 (2H, m), 2.90-2.86 (5H, m), 2.78 (2H, t, J=7.7 Hz), 2.55 (3H, s), 1.74-1.64 (2H, m), 1.35-1.25 (2H, m), 0.84 (3H, t, J=7.3 Hz).

STEP 4. N-[(2-[4-(2-butyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino]carbonyl]-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(2-butyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethylamine (step 3).

MS (ESI) m/z: 520 [(MH)⁺], 518 [(M-H)⁻].

¹H-NMR (CDCl₃) δ: 7.77 (2H, d, J=8.1 Hz), 7.37 (2H, d, J=7.9 Hz), 7.27 (2H, d, J=7.8 Hz), 7.19 (2H, d, J=7.5 Hz), 6.76 (1H, s), 3.57-3.51 (2H, m), 2.92 (2H, t, J=6.6 Hz), 2.88 (3H, s), 2.76 (2H, t, J=7.5 Hz), 2.52 (3H, s), 2.38 (3H, s), 1.73-1.62 (2H, m), 1.36-1.23 (2H, m), 0.82 (3H, t, J=7.3 Hz).

STEP 5. N-[(2-[4-(2-butyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino]carbonyl]-4-methylbenzenesulfonamide mono-p-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from N-[(2-[4-(2-butyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino]carbonyl]-4-methylbenzenesulfonamide (step 4).

¹H-NMR (CDCl₃) δ: 9.85 (1H, br.s), 7.78 (4H, d, J=8.1 Hz), 7.45 (2H, d, J=7.9 Hz), 7.27-7.13 (6H, m), 7.01 (1H, s), 3.45-3.43 (2H, m), 3.03 (3H, s), 2.89-2.87 (2H, m), 2.79-2.73 (5H, m), 2.36 (3H, s), 2.34 (3H, s), 1.74-1.65 (2H, m), 1.35-1.23 (2H, m), 0.84 (3H, t, J=7.2 Hz).

EXAMPLE 240

2-[4-(2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-B]PYRIDIN-3-
YL)PHENYL]-1-METHYLETHYL (4-
METHYLPHENYL)SULFONYLCARBAMATE MONO-HYDROCHLORIDE

To a solution of 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate (Example 7, 694 mg, 1.37 mmol) in methanol (4 ml) was added 10% HCl in methanol (2 ml) at room temperature. This mixture was concentrated, and treated with diethylether to afford 624 mg (90%) of the title compound as a slight yellow solid.

¹H-NMR (DMSO-d₆) δ: 11.92 (1H, br.s), 7.76 (2H, d, J=7.9 Hz), 7.49-7.39 (6H, m), 7.26 (1H, br.s), 4.98-4.88 (1H, m), 2.94-2.83 (4H, m), 2.63 (3H, s), 2.46 (3H, s), 2.34 (3H, s), 1.23 (3H, t, J=7.5 Hz), 1.12 (3H, d, J=6.1 Hz).

MS (ESI) m/z: 507 [(MH)⁺], 505 [(M-H)⁻].

EXAMPLE 241

N-{(2-[4-[5,7-DIMETHYL-2-(3-PHENYLPROPYL)-3H-IMIDAZO[4,5-B]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE

A mixture of N-{(2-[4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl]ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (step 4 of Example 162, 86 mg, 0.19 mmol), 4-phenylbutyric acid (37 mg, 0.23 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (40 mg, 0.21 mmol) was stirred at room temperature for 5 days. The mixture was concentrated to give an orange syrup. This material was dissolved in toluene (8 ml), added p-toluenesulfonic acid mono-hydrate (3 mg, 0.02 mol), then stirred under reflux temperature for 5 h. The mixture was diluted with dichloromethane and washed with diluted hydrochloric acid. The organic layer was concentrated. Purification by TLC developing with hexane/ethyl acetate (1:3) gave 32 mg (29%) of the title compound as a colorless solid.

¹H-NMR (CDCl₃) δ: 7.85 (2H, d, J=8.4 Hz), 7.31-7.01 (11H, m), 6.91 (1H, s), 3.52-3.45 (2H, m), 2.83 (2H, t, J=6.4 Hz), 2.71-2.65 (2H, m), 2.64 (3H, s), 2.58-2.53 (2H, m), 2.41 (3H, s), 2.39 (3H, s), 2.00-1.90 (2H, m).

MS (ESI) m/z: 582 [(MH)⁺], 580 [(M-H)⁻].

5 EXAMPLE 242

N-{(2-{4-[5,7-DIMETHYL-2-(3-OXO-3-PHENYLPROPYL)-3H-IMIDAZO[4,5-B]PYRIDIN-3-YL]PHENYL}ETHYL)AMINO}CARBONYL}-4-METHYLBENZENESULFONAMIDE

The title compound was prepared according to the procedure described in Example 241 from *N*-{[(2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (step 4 of Example 162) and 3-benzoylpropionic acid.

¹H-NMR (CDCl₃) δ: 8.04-7.14 (11H, m), 6.90 (1H, s), 6.20-6.15 (1H, m), 3.50-3.38 (4H, m), 3.03-2.81 (4H, m), 2.56 (3H, s), 2.44 (3H, s), 2.41 (3H, s).

15 MS (ESI) m/z: 596 [(MH)⁺], 594 [(M-H)⁻].

EXAMPLE 243

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL 3-PYRIDINYLSULFONYLCARBAMATE

20 STEP 1. 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl phenyl carbonate

To a stirred solution of 2-[4-(6-Chloro-2-ethyl-5-trifluoromethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4 of Example 104, 3.90 g, 10.6 mmol) in dichloromethane (20 mL) and pyridine (2 ml) was added dropwise phenyl chloroformate (1.6 mL, 12.7 mmol), and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with dichloromethane (50mL), washed with water (50 ml). The organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash column

chromatography eluting with hexane/ethyl acetate (3:1) afforded 4.2 g (82%) of the title compound as a colorless syrup.

^1H NMR (CDCl_3) δ 8.12 (1H, s), 7.53-7.15 (10H, m), 4.56 (2H, t, $J=6.8$ Hz), 3.20 (2H, t, $J=6.8$ Hz), 2.79 (2H, q, $J=7.6$ Hz), 1.36 (3H, t, $J=7.6$ Hz).

5 MS (EI) m/z : 488 (M^+).

STEP 2. 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl 3-pyridinylsulfonfylcarbamate

To a stirred solution of 3-pyridinesulfonamide (Rafik, Karaman; et al., *J. Am. Chem. Soc.*, 1992, 114, 4889, 120 mg, 0.76 mmol) in DMF (3 mL) was added NaH (60% oil dispersion, 27 mg, 0.68 mmol) at room temperature. After 10min., phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylcarbamate (step 1, 313 mg, 0.64 mmol) was added, and the mixture was stirred for 9 h at 80 °C. The mixture was diluted with ethyl acetate (50 mL), and washed with water and brine. The organic layer was dried (Na₂SO₄) and concentrated. Purification by TLC developing with dichloromethane/methanol (6:1) and TLC developing with dichloromethane/methanol (10:1) gave 67 mg (19%) of the title compound as colorless solid.

^1H -NMR (CDCl_3) δ 9.18 (1H, s), 8.73-8.72 (1H, m), 8.32-8.29 (1H, m), 8.09 (1H, s), 7.40-7.15 (6H, m), 4.33-4.29 (2H, m), 2.99-2.94 (2H, m), 2.78-2.71 (2H, m), 1.35-1.32 (3H, m).

MS (ESI) m/z : 553 (MH^+), 551 ($[\text{M}-\text{H}]^-$)

EXAMPLE 244

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL 2-PYRIDINYL SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in step 2 of Example 243 from 2-pyridinesulfonamide (Naito, T.; et al., *Chem.*

Pharm. Bull., 1955, 3, 38) and 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 243).

m.p.: 127.0-130.0 °C

¹H-NMR (CDCl₃) δ 8.76-8.73 (1H, m), 8.24-8.21 (2H, m), 8.16 (1H, s), 8.03-7.97 (1H, m), 7.62-7.56 (1H, m), 7.37 (2H, d, J=8.2 Hz), 7.23 (2H, d, J=8.2 Hz), 7.17 (1H, s), 4.37 (2H, t, J=6.8 Hz), 3.01 (2H, t, J=6.8 Hz), 2.77 (2H, q, J=7.6 Hz), 1.35 (3H, t, J=7.6 Hz).

MS (ESI) m/z: 553 (MH⁺), 551 ([M-H]⁻).

EXAMPLE 245

2-[4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL]ETHYL 4-PYRIDINYLSULFONYLCARBAMATE

The title compound was prepared according to the procedure described in step 2 of Example 243 from 4-pyridinesulfonamide (Comrie, A. M.; et al., *J.*

Chem. Soc., 1958, 3514) and 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 243).

¹H-NMR (CDCl₃) δ 8.82 (2H, d, J=5.2 Hz), 8.10 (1H, s), 7.87 (2H, d, J=4.9 Hz), 7.44 (2H, d, J=7.9 Hz), 7.27 (2H, d, J=7.9 Hz), 7.20 (1H, s), 4.34 (2H, t, J=7.3 Hz), 3.04 (2H, t, J=7.3 Hz), 2.78 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

MS (ESI) m/z: 553 (MH⁺), 551 ([M-H]⁻).

EXAMPLE 246

2-[4-(5-ACETYL-2-ETHYL-1H-BENZIMIDAZOL-1-YL)PHENYL]-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE STEP 1. 1-(4-{[4-(2-hydroxypropyl)phenyl]amino}-3-nitrophenyl)ethanone

The title compound was prepared according to the procedure described in step 1 of Example 162 from 1-(4-chloro-3-nitrophenyl)ethanone and 1-(4-aminophenyl)-2-propanol (step 1 of Example 6).

¹H-NMR (CDCl₃) δ: 9.85 (1H, br.s), 8.83-8.82 (1H, m), 7.99-7.95 (1H, m), 7.33 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.18 (1H, d, J=9.0 Hz), 4.13-4.04 (1H, m), 2.87-2.72 (2H, m), 2.58 (3H, s), 1.29 (3H, d, J=6.2 Hz).

STEP 2. 1-(3-amino-4-{[4-(2-hydroxypropyl)phenyl]amino}phenyl)ethanone

The title compound was prepared according to the procedure described in step 4 of Example 1 from 1-(4-{[4-(2-hydroxypropyl)phenyl]amino}-3-nitrophenyl)ethanone (step 1).

MS (EI) m/z: 284 (M⁺).

STEP 3. 2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1-methylethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-(3-amino-4-{[4-(2-hydroxypropyl)phenyl]amino}phenyl)ethanone (step 2).

¹H-NMR (CDCl₃) δ: 8.41-8.40 (1H, m), 8.83-8.82 (1H, m), 7.92-7.89 (1H, m), 7.43 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.12-7.09 (1H, m), 5.25-5.18 (1H, m), 3.07-2.88 (2H, m), 2.80 (2H, q, J=7.3 Hz), 2.68 (3H, s), 2.34-2.26 (2H, m), 1.37 (3H, q, J=7.5 Hz), 1.32 (3H, d, J=6.2 Hz), 1.10 (3H, t, J=7.5 Hz).

STEP 4. 1-[2-ethyl-1-[4-(2-hydroxypropyl)phenyl]-1H-benzimidazol-5-yl]ethanone

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1-methylethyl propanoate (step 3).

¹H-NMR (CDCl₃) δ: 8.39 (1H, s), 7.89-7.86 (1H, m), 7.47 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 7.13-7.10 (1H, m), 4.23-4.13 (1H, m), 2.94-2.86 (2H, m), 2.80 (2H, q, J=7.5 Hz), 2.66 (3H, s), 1.39-1.33 (6H, m).

STEP 5. 2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 1-{2-ethyl-1-[4-(2-hydroxypropyl)phenyl]-1H-benzimidazol-5-yl}ethanone (step 4).

¹H-NMR (CDCl₃) δ: 8.40 (1H, d, J=1.1 Hz), 7.91-7.86 (3H, m), 7.32-7.24 (4H, m), 7.17 (2H, d, J=7.9 Hz), 7.07 (1H, d, J=8.4 Hz), 5.09-5.03 (1H, m), 2.99-2.75 (2H, m), 2.77 (2H, q, J=7.5 Hz), 2.67 (3H, s), 2.37 (3H, s), 1.33 (3H, t, J=7.5 Hz), 1.21 (3H, d, J=6.1 Hz).

MS (ESI) m/z: 520 (MH⁺), 518 ([M-H]⁻).

EXAMPLE 247

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 1-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-propanol

The title compound was prepared according to the procedure described in step 1 of Example 162 from 2,4-dichloro-5-nitrobenzotrifluoride and 1-(4-aminophenyl)-2-propanol (step 1 of Example 6).

¹H-NMR (CDCl₃) δ: 9.69 (1H, br.s), 8.58 (1H, s), 7.36 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.20 (1H, s), 4.13-4.06 (1H, m), 2.88-2.73 (2H, m), 1.48 (1H, d, J=4.2 Hz), 1.30 (3H, d, J=6.2 Hz).

STEP 2. 1-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-propanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 1-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-propanol (step 1).

¹H-NMR (CDCl₃) δ: 7.17 (1H, s), 7.15 (2H, d, J=8.4 Hz), 7.06 (1H, s), 6.90 (2H, d, J=8.4 Hz), 4.05-3.98 (1H, m), 2.79-2.61 (2H, m), 1.26 (3H, d, J=6.3 Hz).

STEP 3. 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-(4-{[2-amino-5-chloro-4-

5 (trifluoromethyl)phenyl]amino}phenyl)-2-propanol (step 2).

MS (EI) m/z: 438 (M⁺).

STEP 4. 1-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-2-propanol

10 The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl propanoate (step 3).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.47 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 7.21 (1H, s), 4.20-4.10 (1H, m), 2.95-2.83 (2H, m), 2.79 (2H, q, J=7.5 Hz), 1.56 (1H, d, J=4.2 Hz), 1.36 (3H, t, J=7.5 Hz), 1.34 (3H, d, J=6.2 Hz).

15 STEP 5. 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl (4-methylphenyl)sulfonyl carbamate

The title compound was prepared according to the procedure described in Example 3 from 1-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-2-propanol (step 4).

20 ¹H-NMR (CDCl₃) δ: 8.09 (1H, s), 7.87 (2H, d, J=8.4 Hz), 7.41 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.21 (1H, s), 5.06-5.00 (1H, m), 3.04-2.74 (4H, m), 2.40 (3H, s), 1.36 (3H, t, J=7.5 Hz), 1.23 (3H, d, J=6.2 Hz).

MS (ESI) m/z: 580 (MH⁺), 578 ([M-H]⁻).

25 EXAMPLE 248

(1S)-2-[4-(5-ACETYL-2-ETHYL-1H-BENZIMIDAZOL-1-YL)PHENYL]-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

09977761.101501

STEP 1. (2S)-1-(4-nitrophenyl)-2-propanol and (1R)-1-methyl-2-(4-nitrophenyl)ethyl propanoate

To a mixture of 1-(4-nitrophenyl)-2-propanol (Schadt, F. L. et al., *J. Am. Chem. Soc.*, 1978, 100, 228., 2.5 g, 13.8 mmol) and propanoic anhydride (1.8 g, 13.8 mmol) in benzene (34 ml) was added Lipase PS/Celite (0.5 g, Bianchi, D. et al. *J. Org. Chem.* 1988, 53, 5531). The resulting mixture was stirred at room temperature for 72 h. The reaction mixture was filtered through a pad of Celite. The filtrate was washed with saturated aqueous sodium hydrogencarbonate and brine. The organic layer was dried (MgSO₄), and concentrated. Purification by flash column chromatography eluting with hexane/diethyl ether (4:1 to 1:1) afforded 1.91 g (58 %) of (1R)-1-methyl-2-(4-nitrophenyl)ethyl propanoate as a slight yellow oil and 1.14 g (46%) of (2S)-1-(4-nitrophenyl)-2-propanol as a colorless solid (93% e.e.). Recrystallization of 1.14 g of (2S)-1-(4-nitrophenyl)-2-propanol from hexane/diethyl ether afforded 617 mg of a colorless needle (99% e.e.).

(1R)-1-methyl-2-(4-nitrophenyl)ethyl propanoate

¹H-NMR (CDCl₃) δ: 8.16 (2H, d, J=8.8 Hz), 7.37 (2H, d, J=8.8 Hz), 5.22-5.11 (1H, m), 3.04-2.87 (2H, m), 2.30-2.19 (2H, m), 1.26 (3H, d, J=6.1 Hz), 1.07 (3H, t, J=7.5 Hz).

(2S)-1-(4-nitrophenyl)-2-propanol

¹H-NMR (CDCl₃) δ: 8.18 (2H, d, J=8.8 Hz), 7.39 (2H, d, J=8.8 Hz), 4.14-4.04 (1H, m), 2.92-2.79 (2H, m), 1.49 (1H, d, J=4.0 Hz), 1.28 (3H, d, J=6.1 Hz).

[α]_D²³ +31.0° (c 1.00, diethyl ether)

STEP 2. (2S)-1-(4-aminophenyl)-2-propanol

The title compound was prepared according to the procedure described in step 4 of Example 1 from (2S)-1-(4-nitrophenyl)-2-propanol (step 1).

¹H-NMR (CDCl₃) δ: 7.00 (2H, d, J=8.4 Hz), 6.65 (2H, d, J=8.4 Hz), 3.99-3.89 (1H, m), 3.60 (2H, br.s) 2.73-2.52 (2H, m), 1.22 (3H, d, J=6.2 Hz).

STEP 3. 1-[4-({4-[(2S)-2-hydroxypropyl]phenyl}amino)-3-nitrophenyl]ethanone

The title compound was prepared according to the procedure described in step 1 of Example 162 from 1-(4-chloro-3-nitrophenyl)ethanone and (2S)-1-(4-aminophenyl)-2-propanol (step 2).

¹H-NMR (CDCl₃) δ: 9.85 (1H, br.s), 8.83-8.82 (1H, m), 7.99-7.95 (1H, m), 7.33 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.18 (1H, d, J=9.0 Hz), 4.13-4.04 (1H, m), 2.87-2.72 (2H, m), 2.58 (3H, s), 1.29 (3H, d, J=6.2 Hz).

STEP 4. 1-[3-amino-4-({4-[(2S)-2-hydroxypropyl]phenyl}amino)phenyl]ethanone

The title compound was prepared according to the procedure described in step 4 of Example 1 from 1-[4-({4-[(2S)-2-hydroxypropyl]phenyl}amino)-3-nitrophenyl]ethanone (step 3).

MS (EI) m/z: 284 (M⁺).

STEP 5. (1S)-2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1-methylethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-[3-amino-4-({4-[(2S)-2-hydroxypropyl]phenyl}amino)phenyl]ethanone (step 4).

¹H-NMR (CDCl₃) δ: 8.41-8.40 (1H, m), 8.83-8.82 (1H, m), 7.92-7.89 (1H, m), 7.43 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.12-7.09 (1H, m), 5.25-5.18 (1H, m), 3.07-2.88 (2H, m), 2.80 (2H, q, J=7.3 Hz), 2.68 (3H, s), 2.34-2.26 (2H, m), 1.37 (3H, q, J=7.5 Hz), 1.32 (3H, d, J=6.2 Hz), 1.10 (3H, t, J=7.5 Hz).

STEP 6. 1-(2-ethyl-1-[4-[(2S)-2-hydroxypropyl]phenyl]-1H-benzimidazol-5-yl)ethanone

The title compound was prepared according to the procedure described in step 6 of Example 1 from (1S)-2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1-methylethyl propanoate (step 5).

¹H-NMR (CDCl₃) δ: 8.39 (1H, d, J=1.1 Hz), 7.87 (1H, dd, J=8.6, 1.1 Hz), 7.48 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 7.12 (1H, d, J=8.6 Hz), 4.22-4.12 (1H, m), 2.94-2.89 (2H, m), 2.80 (2H, q, J=7.5 Hz), 2.69 (3H, s), 2.42 (1H, br.s), 1.37 (3H, t, J=7.5 Hz), 1.33 (3H, d, J=6.2 Hz).

STEP 7. (1S)-2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 1-(2-ethyl-1-{4-[(2S)-2-hydroxypropyl]phenyl}-1H-benzimidazol-5-yl)ethanone (step 6).

¹H-NMR (CDCl₃) δ: 8.40 (1H, d, J=1.1 Hz), 7.91-7.86 (3H, m), 7.32-7.24 (4H, m), 7.17 (2H, d, J=7.9 Hz), 7.07 (1H, d, J=8.4 Hz), 5.09-5.03 (1H, m), 2.99-2.75 (2H, m), 2.77 (2H, q, J=7.5 Hz), 2.67 (3H, s), 2.37 (3H, s), 1.33 (3H, t, J=7.5 Hz), 1.21 (3H, d, J=6.1 Hz).

MS (ESI) m/z: 520 (MH⁺), 518 ([M-H]⁻).

[α]_D²⁴ -3.09° (c 0.120, methanol)

EXAMPLE 249

(1R)-2-[4-(5-ACETYL-2-ETHYL-1H-BENZIMIDAZOL-1-YL)PHENYL]-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. (2R)-1-(4-nitrophenyl)-2-propanol

To a solution of (1R)-1-methyl-2-(4-nitrophenyl)ethyl propanoate (step 1 of Example 248, 1.91 g, 8.05 mmol) in ethanol (20 ml) was added 2N aqueous NaOH (5 ml) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, extracted with diethyl ether (2 x 50 ml). The organic layer was washed with brine, dried

(MgSO₄), and concentrated. Purification by flash column chromatography eluting with hexane/diethyl ether (1:1) afforded 1.16 g (80 %) of title compound as a colorless solid (79% e.e.). Recrystallization from hexane/diethyl ether afforded 717 mg of a colorless needle (99% e.e.).

¹H-NMR (CDCl₃) δ: 8.18 (2H, d, J=8.8 Hz), 7.39 (2H, d, J=8.8 Hz), 4.14-4.04 (1H, m), 2.92-2.79 (2H, m), 1.49 (1H, d, J=4.0 Hz), 1.28 (3H, d, J=6.1 Hz).
[α]_D²³ -32.6° (c 1.00, diethyl ether)

STEP 2. (2R)-1-(4-aminophenyl)-2-propanol

The title compound was prepared according to the procedure described in step 4 of Example 1 from (2R)-1-(4-nitrophenyl)-2-propanol (step 1).

¹H-NMR (CDCl₃) δ: 7.00 (2H, d, J=8.4 Hz), 6.65 (2H, d, J=8.4 Hz), 3.99-3.89 (1H, m), 3.60 (2H, br.s) 2.73-2.52 (2H, m), 1.22 (3H, d, J=6.2 Hz).

STEP 3. 1-[4-({4-[(2R)-2-hydroxypropyl]phenyl}amino)-3-nitrophenyl]ethanone

The title compound was prepared according to the procedure described in step 1 of Example 162 from 1-(4-chloro-3-nitrophenyl)ethanone and (2R)-1-(4-aminophenyl)-2-propanol (step 2).

¹H-NMR (CDCl₃) δ: 9.85 (1H, br.s), 8.83-8.82 (1H, m), 7.99-7.95 (1H, m), 7.33 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.18 (1H, d, J=9.0 Hz), 4.13-4.04 (1H, m), 2.87-2.72 (2H, m), 2.58 (3H, s), 1.29 (3H, d, J=6.2 Hz).

STEP 4. 1-[3-amino-4-({4-[(2R)-2-hydroxypropyl]phenyl}amino)phenyl]ethanone

The title compound was prepared according to the procedure described in step 4 of Example 1 from 1-[4-({4-[(2R)-2-hydroxypropyl]phenyl}amino)-3-nitrophenyl]ethanone (step 3).

MS (EI) m/z: 284 (M⁺).

STEP 5. (1R)-2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1-methylethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-[3-amino-4-({4-[(2R)-2-

- 5 hydroxypropyl]phenyl}amino)phenyl]ethanone (step 4).

¹H-NMR (CDCl₃) δ: 8.41-8.40 (1H, m), 8.83-8.82 (1H, m), 7.92-7.89 (1H, m), 7.43 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.12-7.09 (1H, m), 5.25-5.18 (1H, m), 3.07-2.88 (2H, m), 2.80 (2H, q, J=7.3 Hz), 2.68 (3H, s), 2.34-2.26 (2H, m), 1.37 (3H, q, J=7.5 Hz), 1.32 (3H, d, J=6.2 Hz), 1.10 (3H, t, J=7.5 Hz).

- 10 STEP 6. 1-(2-ethyl-1-{4-[(2R)-2-hydroxypropyl]phenyl}-1H-benzimidazol-5-yl)ethanone

The title compound was prepared according to the procedure described in step 6 of Example 1 from (1R)-2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1-methylethyl propanoate (step 5).

- 15 ¹H-NMR (CDCl₃) δ: 8.39 (1H, d, J=1.1 Hz), 7.87 (1H, dd, J=8.6, 1.1 Hz), 7.48 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 7.12 (1H, d, J=8.6 Hz), 4.22-4.12 (1H, m), 2.94-2.89 (2H, m), 2.80 (2H, q, J=7.5 Hz), 2.69 (3H, s), 2.42 (1H, br.s), 1.37 (3H, t, J=7.5 Hz), 1.33 (3H, d, J=6.2 Hz).

- 20 STEP 7. (1R)-2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 1-(2-ethyl-1-{4-[(2R)-2-hydroxypropyl]phenyl}-1H-benzimidazol-5-yl)ethanone (step 6).

- 25 ¹H-NMR (CDCl₃) δ: 8.40 (1H, d, J=1.1 Hz), 7.91-7.86 (3H, m), 7.32-7.24 (4H, m), 7.17 (2H, d, J=7.9 Hz), 7.07 (1H, d, J=8.4 Hz), 5.09-5.03 (1H, m), 2.99-2.75 (2H, m), 2.77 (2H, q, J=7.5 Hz), 2.67 (3H, s), 2.37 (3H, s), 1.33 (3H, t, J=7.5 Hz), 1.21 (3H, d, J=6.1 Hz).

MS (ESI) m/z: 520 (MH^+), 518 ($[\text{M}-\text{H}]^-$).

$[\alpha]_D^{24} +6.05^\circ$ (c 0.118, methanol).

EXAMPLE 250

(1S)-2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-

5 BENZIMIDAZOL-1-YL]PHENYL}-1-METHYLETHYL (4-

METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. (2S)-1-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)-
2-propanol

10 The title compound was prepared according to the procedure described
in step 1 of Example 162 from 2,4-dichloro-5-nitrobenzotrifluoride and (2S)-1-(4-aminophenyl)-2-propanol (step 2 of Example 248).

$^1\text{H-NMR}$ (CDCl_3) δ : 9.69 (1H, br.s), 8.58 (1H, s), 7.36 (2H, d, $J=8.4$ Hz), 7.24 (2H, d, $J=8.4$ Hz), 7.20 (1H, s), 4.13-4.06 (1H, m), 2.88-2.73 (2H, m), 1.48 (1H, d, $J=4.2$ Hz), 1.30 (3H, d, $J=6.2$ Hz).

15 STEP 2. (2S)-1-(4-{[2-amino-5-chloro-4-
(trifluoromethyl)phenyl]amino}phenyl)-2-propanol

The title compound was prepared according to the procedure described
in step 2 of Example 28 from (2S)-1-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-propanol (step 1).

20 $^1\text{H-NMR}$ (CDCl_3) δ : 7.17 (1H, s), 7.15 (2H, d, $J=8.4$ Hz), 7.06 (1H, s), 6.90 (2H, d, $J=8.4$ Hz), 4.05-3.98 (1H, m), 2.79-2.61 (2H, m), 1.26 (3H, d, $J=6.3$ Hz).

STEP 3. (1S)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-
yl]phenyl}-1-methylethyl propanoate

25 The title compound was prepared according to the procedure described
in step 5 of Example 1 from (2S)-1-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-propanol (step 2).

MS (EI) m/z: 438 (M^+).

STEP 4. (2S)-1-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-2-propanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from (1S)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl propanoate (step 3).

$^1\text{H-NMR}$ (CDCl_3) δ : 8.12 (1H, s), 7.47 (2H, d, $J=8.4$ Hz), 7.28 (2H, d, $J=8.4$ Hz), 7.21 (1H, s), 4.20-4.10 (1H, m), 2.95-2.83 (2H, m), 2.79 (2H, q, $J=7.5$ Hz), 1.56 (1H, d, $J=4.2$ Hz), 1.36 (3H, t, $J=7.5$ Hz), 1.34 (3H, d, $J=6.2$ Hz).

STEP 5. (1S)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from (2S)-1-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-2-propanol (step 4).

m.p.: 200.3 °C

$^1\text{H-NMR}$ (CDCl_3) δ : 8.09 (1H, s), 7.87 (2H, d, $J=8.4$ Hz), 7.41 (2H, d, $J=8.4$ Hz), 7.31 (2H, d, $J=8.4$ Hz), 7.24 (2H, d, $J=8.4$ Hz), 7.21 (1H, s), 5.06-5.00 (1H, m), 3.04-2.74 (4H, m), 2.40 (3H, s), 1.36 (3H, t, $J=7.5$ Hz), 1.23 (3H, d, $J=6.2$ Hz).

MS (ESI) m/z : 580 (MH^+), 578 ($[\text{M}-\text{H}]^-$).

$[\alpha]_D^{24} +1.31^\circ$ (c 0.398, methanol)

ee: 98%.

EXAMPLE 251

(1S)-2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE MONO-P-TOLUENESULFONATE

The title compound was prepared according to the procedure described in Example 231 from (1S)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl (4-methylphenyl)sulfonylcarbamate (step 5 of Example 250).

- 5 ¹H-NMR (DMSO-d₆) δ: 11.91 (1H, br.s), 8.23 (1H, s), 7.75 (2H, d, J=8.3 Hz), 7.50-7.37 (9H, m), 7.11 (2H, d, J=8.1 Hz), 4.97-4.91 (1H, m), 2.92-2.76 (4H, m), 2.30 (3H, s), 2.27 (3H, s), 1.24 (3H, t, J=7.3 Hz), 1.14 (3H, d, J=6.2 Hz).
MS (ESI) m/z: 580 (MH⁺), 578 ([M-H]⁻).

EXAMPLE 252

- 10 (1R)-2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. (2R)-1-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-propanol

- 15 The title compound was prepared according to the procedure described in step 1 of Example 162 from 2,4-dichloro-5-nitrobenzotrifluoride and (2R)-1-(4-aminophenyl)-2-propanol (step 2 of Example 249).

- ¹H-NMR (CDCl₃) δ: 9.69 (1H, br.s), 8.58 (1H, s), 7.36 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.20 (1H, s), 4.13-4.06 (1H, m), 2.88-2.73 (2H, m), 1.48 (1H, d, J=4.2 Hz), 1.30 (3H, d, J=6.2 Hz).

- 20 STEP 2. (2R)-1-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-propanol

- The title compound was prepared according to the procedure described in step 2 of Example 28 from (2R)-1-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-propanol (step 1).

- 25 ¹H-NMR (CDCl₃) δ: 7.17 (1H, s), 7.15 (2H, d, J=8.4 Hz), 7.06 (1H, s), 6.90 (2H, d, J=8.4 Hz), 4.05-3.98 (1H, m), 2.79-2.61 (2H, m), 1.26 (3H, d, J=6.3 Hz).

STEP 3. (1R)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from (2R)-1-(4-{[2-amino-5-chloro-4-

5 (trifluoromethyl)phenyl]amino}phenyl)-2-propanol (step 2).

MS (EI) m/z: 438 (M⁺).

STEP 4. (2R)-1-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-2-propanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from (1R)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl propanoate (step 3).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.47 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 7.21 (1H, s), 4.20-4.10 (1H, m), 2.95-2.83 (2H, m), 2.79 (2H, q, J=7.5 Hz), 1.56 (1H, d, J=4.2 Hz), 1.36 (3H, t, J=7.5 Hz), 1.34 (3H, d, J=6.2 Hz).

STEP 5. (1R)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl (4-methylphenyl)sulfonyl carbamate

The title compound was prepared according to the procedure described in Example 3 from (2R)-1-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-2-propanol (step 4).

m.p.: 199.9 °C

¹H-NMR (CDCl₃) δ: 10.70 (1H, br.s), 8.10 (1H, s), 7.89 (2H, d, J=8.3 Hz), 7.40 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.3 Hz), 7.22 (2H, d, J=8.3 Hz), 7.20 (1H, s), 5.32-5.00 (1H, m), 3.04-2.82 (2H, m), 2.78 (2H, q, J=7.5 Hz), 2.40 (3H, s), 1.36 (3H, t, J=7.5 Hz), 1.23 (3H, d, J=6.2 Hz).

MS (ESI) m/z: 580 (MH⁺), 578 ([M-H]⁻).

[α]_D²⁴ -2.19° (c 0.402, methanol)

ee: 97%.

EXAMPLE 253

N-{[(2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl)amino]carbonyl}-4-

5 METHYLBENZENESULFONAMIDE

STEP 1. 1-[4-(2-azidopropyl)phenyl]-6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazole

To a stirred solution of 1-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]-2-propanol (step 8 of Example 247, 1.96 g, 5.12
10 mmol), triphenylphosphine (1.75 g, 6.66 mmol) and diphenylphosphoryl azide (1.83 mg, 6.66 mmol) in tetrahydrofuran (15 ml) was added diethyl azodicarboxylate (1.16 mg, 6.66 mmol) at room temperature. The resulting mixture was stirred at temperature for 3 h, then under reflux temperature. The mixture was diluted with ethyl acetate and washed with water and brine. The
15 organic layer was dried (Na₂SO₄), and concentrated. Purification by flash column chromatography eluting with hexane/ethyl acetate (2:1) and TLC developing with hexane/ethyl acetate (1:1) afforded 769 mg (37%) of the title compound as a slight yellow syrup.

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.47 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.3
20 Hz), 7.21 (1H, s), 3.85-3.77 (1H, m), 2.92-2.89 (2H, m), 2.80 (2H, q, J=7.5 Hz), 1.37 (3H, d, J=6.6 Hz), 1.36 (3H, t, J=7.5 Hz).

MS (ESI) m/z: 408 (MH⁺).

STEP 2. 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethylamine

25 The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidopropyl)phenyl]-6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazole (step 1).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.44 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 7.21 (1H, s), 3.49-3.26 (1H, m), 2.86-2.95 (2H, m), 2.79 (2H, q, J=7.5 Hz), 1.36 (3H, t, J=7.5 Hz), 1.20 (3H, d, J=6.2 Hz).

STEP 3. N-{[(2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl)amino]carbonyl}-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethylamine (step 2).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.73 (2H, d, J=8.4 Hz), 7.41 (2H, d, J=8.3 Hz), 7.29-7.23 (4H, m), 7.17 (1H, s), 4.20-4.11 (1H, m), 2.99-2.82 (2H, m), 2.78 (2H, q, J=7.3 Hz), 2.38 (3H, s), 1.35 (3H, t, J=7.3 Hz), 1.24 (3H, d, J=6.6 Hz). MS (ESI) m/z: 579 (MH⁺), 577 ([M-H]⁻).

EXAMPLE 254

N-{[[(1S)-2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}-1-METHYLETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE

STEP 1. 1-[4-[(2s)-2-azidopropyl]phenyl]-6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 1 of Example 253 from (2R)-1-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-2-propanol (step 4 of Example 252).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.46 (2H, d, J=7.9 Hz), 7.29 (2H, d, J=7.9 Hz), 7.21 (1H, s), 3.84-3.77 (1H, m), 2.92-2.89 (2H, m), 2.79 (2H, q, J=7.6 Hz), 1.39-1.33 (6H, m).

STEP 2. (1S)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-[(2S)-2-azidopropyl]phenyl]-6-chloro-2-ethyl-

- 5 5-(trifluoromethyl)-1H-benzimidazole (step 1).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.44 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 7.21 (1H, s), 3.49-3.26 (1H, m), 2.86-2.65 (2H, m), 2.79 (2H, q, J=7.5 Hz), 1.36 (3H, t, J=7.5 Hz), 1.20 (3H, d, J=6.2 Hz).

- 10 STEP 3. N-{[[(1S)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl]amino]carbonyl}-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from (1S)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethylamine (step 2).

m.p.: 141.0-143.0 °C

- 15 ¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.73 (2H, d, J=8.3 Hz), 7.41 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.3 Hz), 7.25 (2H, d, J=8.3 Hz), 7.17 (1H, s), 6.58 (1H, d, J=7.7 Hz), 4.22-4.14 (1H, m), 2.82-2.30 (2H, m), 2.78 (2H, q, J=7.6 Hz), 2.39 (3H, s), 1.35 (3H, t, J=7.5 Hz), 1.24 (3H, d, J=6.6 Hz).
MS (ESI) m/z: 579 (MH⁺), 691 ([M+CF₃COOH-H]⁺).

- 20 [α]_D²⁴ -5.08° (c 0.394, methanol)
ee: 99%.

EXAMPLE 255

- 25 N-{[[(1R)-2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}-1-METHYLETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE

STEP 1. 1-[4-[(2R)-2-azidopropyl]phenyl]-6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 1 of Example 253 from (2S)-1-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]-2-propanol (step 4 of Example 250).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.46 (2H, d, J=7.9 Hz), 7.29 (2H, d, J=7.9 Hz), 7.21 (1H, s), 3.84-3.77 (1H, m), 2.92-2.89 (2H, m), 2.79 (2H, q, J=7.6 Hz), 1.39-1.33 (6H, m).

STEP 2. (1R)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-[(2R)-2-azidopropyl]phenyl]-6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazole (step 1).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.44 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 7.21 (1H, s), 3.49-3.26 (1H, m), 2.86-2.65 (2H, m), 2.79 (2H, q, J=7.5 Hz), 1.36 (3H, t, J=7.5 Hz), 1.20 (3H, d, J=6.2 Hz).

STEP 3. N-[[[(1R)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethyl]amino]carbonyl]-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from (1R)-2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-methylethylamine (step 2).

m.p.: 138.0-141.0 °C

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.73 (2H, d, J=8.3 Hz), 7.41 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.3 Hz), 7.25 (2H, d, J=8.3 Hz), 7.17 (1H, s), 6.58 (1H, d, J=7.7 Hz), 4.22-4.14 (1H, m), 2.82-2.30 (2H, m), 2.78 (2H, q, J=7.6 Hz), 2.39 (3H, s), 1.35 (3H, t, J=7.5 Hz), 1.24 (3H, d, J=6.6 Hz).

MS (ESI) m/z: 579 (MH⁺), 691 ([M+CF₃COOH-H]⁺).

$[\alpha]_D^{24} +3.43^\circ$ (c 0.408, methanol)

ee: 99%.

EXAMPLE 256

2-{4-[6-CHLORO-2-(1H-PYRAZOL-3-YL)-5-(TRIFLUOROMETHYL)-1H-

5 BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl} ethanol

A mixture of 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl) ethanol (step 2 of Example 104, 2.28 g, 5.85 mmol) and 1H-pyrazole-3-carbaldehyde (562 mg, 2.85 mmol) in ethanol (35 ml) was stirred under reflux temperature for 1 h. The mixture was concentrated and dissolved in benzene (40 ml). To this solution was added lead tetraacetate (2.85 g, 6.44 mmol) at rt. After stirring at room temperature for 18 h, to the mixture were added saturated aqueous sodium hydrogencarbonate (50 ml) and ethyl acetate. The organic layer was separated and washed with brine, dried (Na₂SO₄) and concentrated. Purification by flash column chromatography eluting with dichloromethane/methanol (20:1 to 10:1), then dichloromethane/2-propanol (5:1) afforded 979 mg (41%) of the title compound as a slight brown solid.

¹H-NMR (CDCl₃/CD₃OD = 4/1) δ: 8.12 (1H, br.s), 7.74 (1H, s), 7.59 (1H, br.s), 7.47 (2H, d, J=7.9 Hz), 7.34-7.30 (3H, m), 6.36 (1H, br.s), 3.87 (2H, br.t, J=6.8 Hz), 2.95 (2H, t, J=6.8 Hz).

MS (ESI) m/z: 407 (MH⁺), 405 ([M-H]⁻).

25 STEP 2. 2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl} ethyl (4-methylphenyl)sulfonylcarbamate

099777.1.101501

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol (step 1).

¹H-NMR (CDCl₃) δ: 8.18 (1H, s), 7.91 (2H, d, J=8.3 Hz), 7.54-7.53 (1H, m), 7.34-7.23 (8H, m), 6.31 (1H, br.s), 4.40 (2H, t, J=6.4 Hz), 3.01 (2H, t, J=6.4 Hz), 2.42 (3H, s).

MS (ESI) m/z: 604 (MH⁺), 602 ([M-H]⁻).

EXAMPLE 257

2-[4-[6-CHLORO-2-(1H-PYRAZOL-3-YL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE MONO-P-TOLUENESULFONATE

The title compound was prepared according to the procedure described in Example 231 from 2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (step 2 of Example 256).

¹H-NMR (DMSO-d₆) δ: 8.24 (1H, s), 7.77-7.74 (2H, m), 7.48-7.38 (10H, m), 7.26 (1H, s), 7.11 (2H, d, J=7.9 Hz), 6.44 (1H, br.s), 4.30-4.20 (2H, m), 2.98-2.93 (2H, m), 2.33 (3H, s), 2.27 (3H, s).

MS (ESI) m/z: 604 (MH⁺), 602 ([M-H]⁻).

EXAMPLE 258

(1S)-2-[4-(2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-B]PYRIDIN-3-YL)PHENYL]-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE MONO-HYDROCHLORIDE
STEP 1. (2S)-1-[4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl]-2-propanol

The title compound was prepared according to the procedure described in step 1 of Example 162 from 2-chloro-4,6-dimethyl-3-nitropyridine (step 2 of Example 1) and (2S)-1-(4-aminophenyl)-2-propanol (step 2 of Example 248).

¹H-NMR (CDCl₃) δ: 9.58 (1H, br.s), 7.59 (2H, d, J=8.6 Hz), 7.19 (2H, d, J=8.6 Hz), 6.53 (1H, s), 4.05-3.98 (1H, m), 2.82-2.63 (2H, m), 2.55 (3H, s), 2.43 (3H, s), 1.26 (3H, d, J=6.3 Hz).

STEP 2. (2S)-1-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}-2-propanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from (2S)-1-{4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}-2-propanol (step 1).

¹H-NMR (CDCl₃) δ: 7.13-7.07 (4H, m), 6.60 (1H, s), 6.21 (1H, br.s), 4.02-3.91 (1H, m), 3.26 (2H, br.s), 2.77-2.57 (2H, m), 2.37 (3H, s), 2.20 (3H, s), 1.24 (3H, d, J=6.1 Hz).

STEP 3. (1S)-2-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from (2S)-1-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}-2-propanol (step 2).

MS (EI) m/z: 365 (M⁺).

STEP 4. (2S)-1-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-2-propanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from (1S)-2-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl propanoate (step 3).

¹H-NMR (CDCl₃) δ: 7.42 (2H, d, J=8.4 Hz), 7.35 (2H, d, J=8.4 Hz), 6.91 (1H, s), 4.18-4.05 (1H, m), 2.92-2.75 (4H, m), 2.66 (3H, s), 2.52 (3H, s), 1.34-1.25 (6H, m).

STEP 5. (1S)-2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from (2S)-1-[4-(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-2-propanol (step 4).

¹H-NMR (CDCl₃) δ: 7.92 (2H, d, J=8.2 Hz), 7.33 (2H, d, J=8.2 Hz), 7.30-7.26 (4H, m), 5.14-5.02 (1H, m), 2.99-2.77 (4H, m), 2.66 (3H, s), 2.51 (3H, s), 2.42 (3H, s), 1.29-1.23 (6H, m).

MS (ESI) m/z: 507 (MH⁺), 505 [(M-H)⁻].

STEP 6. 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate mono-hydrochloride

The title compound was prepared according to the procedure described in Example 240 from (1S)-2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate (step 5).

¹H-NMR (DMSO-d₆) δ: 11.92 (1H, br.s), 7.76 (2H, d, J=7.9 Hz), 7.49-7.39 (6H, m), 7.26 (1H, br.s), 4.98-4.88 (1H, m), 2.94-2.83 (4H, m), 2.63 (3H, s), 2.46 (3H, s), 2.34 (3H, s), 1.23 (3H, t, J=7.5 Hz), 1.12 (3H, d, J=6.1 Hz).

MS (ESI) m/z: 507 [(MH)⁺], 505 [(M-H)⁻].

[α]_D²⁴ -12.49° (c 1.014, methanol)

EXAMPLE 259

2-[4-(6-ACETYL-2-ETHYL-3H-IMIDAZO[4,5-B]PYRIDIN-3-YL)PHENYL]-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 1-[6-(4-[2-hydroxypropyl]phenyl)amino]-5-nitro-3-pyridinyl]ethanone

The title compound was prepared according to the procedure described in step 1 of Example 162 from 1-(6-chloro-5-nitro-3-pyridinyl)ethanone (Paul, B. et al. *J. Med. Chem.*, 1990, 33, 2231-2239.) and 1-(4-aminophenyl)-2-propanol (step 1 of Example 6).

¹H-NMR (CDCl₃) δ: 10.37 (1H, br.s), 9.06-9.03 (2H, m), 7.60 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 4.10-4.00 (1H, m), 2.86-2.69 (2H, m), 2.60 (3H, s), 1.53 (1H, d, J=4.0 Hz), 1.28 (3H, d, J=6.2 Hz).

MS (EI) m/z: 315 (M⁺).

STEP 2. 1-[5-amino-6-(4-[(2-hydroxypropyl)phenyl]amino)-3-pyridinyl]ethanone

To a solution of 1-[6-(4-[2-hydroxypropyl]phenyl)amino)-5-nitro-3-pyridinyl]ethanone (step 1, 1.54 g, 4.88 mmol) in tetrahydrofuran (10 ml) and ethanol (30 ml) was added 10% palladium on carbon (150 mg). The resulting mixture was stirred for 19 h under hydrogen atmosphere. The mixture was filtered through a pad of Celite and the filtrate was concentrated to afford 1.74 g (100%) of the title compound as green syrup.

¹H-NMR (CDCl₃) δ: 8.46 (1H, d, J=1.8 Hz), 7.56 (1H, d, J=1.8 Hz), 7.50 (2H, d, J=8.3 Hz), 7.20 (2H, d, J=8.3 Hz), 6.85 (1H, br.s), 3.76-3.67 (1H, m), 3.38 (2H, br.s), 2.81-2.62 (2H, m), 2.53 (3H, s), 1.26 (3H, d, J=6.1 Hz).

STEP 3. 2-[4-(6-acetyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-[5-amino-6-(4-[(2-hydroxypropyl)phenyl]amino)-3-pyridinyl]ethanone (step 2).

MS (EI) m/z: 379 (M⁺).

STEP 4. 1-(2-ethyl-3-[4-[2-hydroxypropyl]phenyl]-3H-imidazo[4,5-b]pyridin-6-yl)ethanone

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-acetyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl propanoate (step 3).

¹H-NMR (CDCl₃) δ: 8.93 (1H, d, J=1.8 Hz), 8.59 (1H, d, J=1.8 Hz), 7.48 (2H, d, J=8.3 Hz), 7.36 (2H, d, J=8.3 Hz), 4.18-4.08 (1H, m), 2.94-2.80 (2H, m), 2.68 (3H, s), 1.39 (3H, t, J=7.5 Hz), 1.33 (3H, d, J=6.2 Hz).

STEP 5. 2-[4-(6-acetyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 1-(2-ethyl-3-{4-[2-hydroxypropyl]phenyl}-3H-imidazo[4,5-b]pyridin-6-yl)ethanone (step 4).

¹H-NMR (CDCl₃) δ: 8.93 (1H, d, J=1.8 Hz), 8.60 (1H, d, J=1.8 Hz), 7.92 (2H, d, J=8.4 Hz), 7.38-7.29 (6H, m), 5.12-5.03 (1H, m), 3.03-2.82 (4H, m), 2.69 (3H, s), 2.43 (3H, s), 1.28-1.24 (6H, m).

MS (ESI) m/z: 521 [(MH)⁺], 519 [(M-H)].

EXAMPLE 260

(1S)-2-[4-(6-ACETYL-2-ETHYL-3H-IMIDAZO[4,5-B]PYRIDIN-3-YL)PHENYL]-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 1-[6-({4-[(2S)-2-hydroxypropyl]phenyl}amino)-5-nitro-3-pyridinyl]ethanone

The title compound was prepared according to the procedure described in step 1 of Example 162 from 1-(6-chloro-5-nitro-3-pyridinyl)ethanone (Paul, B. et al. *J. Med. Chem.*, 1990, 33, 2231-2239.) and (2S)-1-(4-aminophenyl)-2-propanol (step 2 of Example 248).

¹H-NMR (CDCl₃) δ: 10.37 (1H, br.s), 9.06-9.03 (2H, m), 7.60 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 4.10-4.00 (1H, m), 2.86-2.69 (2H, m), 2.60 (3H, s), 1.53 (1H, d, J=4.0 Hz), 1.28 (3H, d, J=6.2 Hz).

STEP 2. 1-[5-amino-6-(4-[(2S)-2-hydroxypropyl]phenyl)amino]-3-

5 pyridinyl]ethanone

The title compound was prepared according to the procedure described in step 2 of Example 259 from 1-[6-(4-[(2S)-2-hydroxypropyl]phenyl) amino]-5-nitro-3-pyridinyl]ethanone (step 1).

10 ¹H-NMR (CDCl₃) δ: 8.46 (1H, d, J=1.8 Hz), 7.56 (1H, d, J=1.8 Hz), 7.50 (2H, d, J=8.3 Hz), 7.20 (2H, d, J=8.3 Hz), 6.85 (1H, br.s), 3.76-3.67 (1H, m), 3.38 (2H, br.s), 2.81-2.62 (2H, m), 2.53 (3H, s), 1.26 (3H, d, J=6.1 Hz).

STEP 3. (1S)-2-[4-(6-acetyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl propanoate

15 The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-[5-amino-6-(4-[(2S)-2-hydroxypropyl]phenyl) amino]-3-pyridinyl]ethanone (step 2).

MS (EI) m/z: 379 (M⁺).

STEP 4. 1-(2-ethyl-3-{4-[(2S)-2-hydroxypropyl]phenyl}-3H-imidazo[4,5-b]pyridin-6-yl)ethanone

20 The title compound was prepared according to the procedure described in step 6 of Example 1 from (1S)-2-[4-(6-acetyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl propanoate (step 3).

25 ¹H-NMR (CDCl₃) δ: 8.93 (1H, d, J=1.8 Hz), 8.59 (1H, d, J=1.8 Hz), 7.48 (2H, d, J=8.3 Hz), 7.36 (2H, d, J=8.3 Hz), 4.18-4.08 (1H, m), 2.94-2.80 (2H, m), 2.68 (3H, s), 1.39 (3H, t, J=7.5 Hz), 1.33 (3H, d, J=6.2 Hz).

STEP 5. (1S)-2-[4-(6-acetyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 1-(2-ethyl-3-{4-[(2S)-2-hydroxypropyl]phenyl}-3H-imidazo[4,5-b]pyridin-6-yl)ethanone (step 4).

¹H-NMR (CDCl₃) δ: 8.93 (1H, d, J=1.8 Hz), 8.60 (1H, d, J=1.8 Hz), 7.92 (2H, d, J=8.4 Hz), 7.38-7.29 (6H, m), 5.12-5.03 (1H, m), 3.03-2.82 (4H, m), 2.69 (3H, s), 2.43 (3H, s), 1.28-1.24 (6H, m).

MS (ESI) m/z: 521 [(MH)⁺], 519 [(M-H)⁻].

EXAMPLE 261

(1S)-2-[4-(6-ACETYL-2-ETHYL-3H-IMIDAZO[4,5-B]PYRIDIN-3-YL)PHENYL]-1-METHYLETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE MONO-P-TOLUENESULFONATE

The title compound was prepared according to the procedure described in Example 231 from (1S)-2-[4-(6-acetyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl (4-methylphenyl)sulfonylcarbamate (step 5 of Example 260).

¹H-NMR (DMSO-d₆) δ: 11.93 (1H, br.s), 8.90 (1H, d, J=1.8 Hz), 8.63 (1H, d, J=1.8 Hz), 7.76 (2H, d, J=8.4 Hz), 7.38-7.29 (8H, m), 7.11 (2H, d, J=8.4 Hz), 4.96-4.87 (1H, m), 2.90-2.79 (4H, m), 2.32 (3H, s), 2.27 (3H, s), 1.26 (3H, t, J=7.5 Hz), 1.12 (3H, d, J=6.2 Hz).

MS (ESI) m/z: 521 [(MH)⁺], 519 [(M-H)⁻].

[α]_D²⁴ -8.17° (c 1.020, methanol)

EXAMPLE 262

2-{4-[6-CHLORO-2-(2-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE MONO-P-TOLUENESULFONATE

STEP 1. 2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1*h*-benzimidazol-1-yl]phenyl}ethanol

A mixture of 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethanol (1.83 g, 5.54 mmol), 2-pyridinecarboxaldehyde (0.53 ml, 5.54 mmol), and EtOH (40 ml) was refluxed for 1 hour. After cooling to room temperature, the solvent was removed. The residue was dissolved with benzene (50 ml) and treated with Pb(OAc)₄ (3.38 g, 6.10 mmol) at room temperature for 1 hour. The mixture was diluted with EtOAc and the solution was washed with sat. NaHCO₃ aq. and brine. The organic fraction was dried over MgSO₄, then filtered. After evaporation in vacuo, the residue was purified by silica-gel column chromatography eluting with hexane/EtOAc = 5/2 to afford 1.20 g (52%) of the title compound.

¹H-NMR (CDCl₃) δ: 8.42-8.39 (1H, m), 8.23 (1H, s), 8.10-8.07 (1H, m), 7.79-7.75 (1H, m), 7.40-7.23 (6H, m), 3.97 (2H, t, J=6.6 Hz), 2.99 (2H, t, J=6.6 Hz)

MS (ESI) m/z: 418 ([M+H]⁺), 476 ([M+CF₃CO₂]⁺)

STEP 2. 2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1*h*-benzimidazol-1-yl]phenyl}ethyl(4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in example 3 from 2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1*h*-benzimidazol-1-yl]phenyl}ethanol.

¹H-NMR (CDCl₃) δ: 8.39-8.37 (1H, m), 8.23 (1H, s), 8.10-8.06 (1H, m), 7.92-7.87 (2H, m), 7.81-7.76 (1H, m), 7.33-7.18 (8H, m), 4.35 (2H, t, J=6.8 Hz), 2.98 (2H, t, J=6.8 Hz), 2.41 (3H, s)

MS (ESI) m/z: 615 ([M+H]⁺), 613 ([M-H]⁻)

EXAMPLE 263

2-{4-[6-CHLORO-2-(2-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-

METHYLPHENYL)SULFONYLCARBAMATE MONO-P-
TOLUENESULFONATE

The title compound was prepared according to the procedure described in Example 231 from 2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-

5 benzimidazol-1-yl]phenyl}ethyl(4-methylphenyl)sulfonylcarbamate.

MS (ESI) m/z: 615 ([M+H]⁺)

EXAMPLE 264

N-{[(2-{4-[6-CHLORO-2-(2-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-
BENZIMIDAZOL-1-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-

10 METHYLBENZENESULFONAMIDE MONO-P-TOLUENESULFONATE

STEP 1. 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-(2-pyridinyl)-5-
(trifluoromethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-

15 1H-benzimidazol-1-yl]phenyl} ethanol (step 1 of Example 262).

¹H-NMR (CDCl₃) δ: 8.41-8.39 (1H, m), 8.24 (1H, s), 8.11 (1H, d, J=8.8 Hz), 7.82-7.76 (1H, m), 7.38 (2H, d, J=8.4 Hz), 7.35 (1H, s), 7.30-7.25 (3H, m), 3.31 (2H, t, J=7.2 Hz), 3.19 (2H, t, J=7.2 Hz).

STEP 2. 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-(2-pyridinyl)-5-

20 (trifluoromethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 8 of Example 1 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazole (step 1).

¹H-NMR (CDCl₃) δ: 8.40-8.39 (1H, m), 8.24 (1H, s), 8.10 (1H, d, J=7.9 Hz), 7.81-7.75 (1H, m), 7.39 (2H, d, J=8.4 Hz), 7.34 (1H, s), 7.29-7.25 (3H, m), 3.61 (2H, t, J=6.8 Hz), 3.01 (2H, t, J=6.8 Hz).

STEP 3. 2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazole (step 2).

¹H-NMR (CDCl₃) δ: 8.37-8.36 (1H, m), 8.19 (1H, s), 8.03-8.00 (1H, m), 7.78-7.71 (1H, m), 7.32-7.18 (6H, m), 3.02 (2H, t, J=6.8 Hz), 2.82 (2H, t, J=6.8 Hz), 2.17 (2H, br.s).

STEP 4. N-{[(2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-

benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethylamine (step 3).

¹H-NMR (CDCl₃) δ: 8.42-8.39 (1H, m), 8.24 (1H, s), 8.10 (1H, d, J=8.1 Hz), 7.81-7.75 (1H, m), 7.69 (2H, d, J=8.3 Hz), 7.33-7.24 (8H, m), 6.72-6.69 (1H, m), 3.63-3.56 (2H, m), 2.93 (2H, t, J=6.8 Hz), 2.38 (3H, s).

MS (ESI) m/z: 614 [(MH)⁺], 612 [(M-H)].

STEP 5. N-{[(2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide
mono-p-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from N-{[(2-{4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (step 4).

¹H-NMR (DMSO-d₆) δ: 10.63 (1H, br.s), 8.41-8.39 (1H, m), 8.35 (1H, s), 8.08-7.95 (2H, m), 7.75 (2H, d, J=8.3 Hz), 7.49 (2H, d, J=8.3 Hz), 7.44-7.27 (8H, m),

7.10 (2H, d, J=7.7 Hz), 6.61-6.57 (1H, m), 3.30-3.23 (2H, m), 2.74 (2H, t, J=7.0 Hz), 2.31 (3H, s), 2.27 (3H, s).

MS (ESI) m/z: 614 [(MH)⁺], 612 [(M-H)].

EXAMPLE 265

5 N-{[(2-{4-[6-CHLORO-2-(1H-PYRAZOL-3-YL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE MONO-P-TOLUENESULFONATE
STEP 1. 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-(1H-pyrazol-3-yl)-5-
(trifluoromethyl)-1H-benzimidazole

10 The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol (step 1, Example 255).
¹H-NMR (DMSO-d₆) δ: 13.29 (1H, s), 8.25 (1H, s), 7.83-7.81 (1H, m), 7.52-7.43 (4H, m), 7.23 (1H, s), 6.67-6.65 (1H, m), 3.95 (2H, t, J=7.0 Hz), 3.16 (2H, t, J=7.0 Hz).

15 STEP 2. 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-(1H-pyrazol-3-yl)-5-
(trifluoromethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 8 of Example 1 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazole (step 1).

20 ¹H-NMR (DMSO-d₆) δ: 13.27 (1H, s), 8.25 (1H, s), 7.82 (1H, s), 7.52-7.43 (4H, m), 7.21 (1H, s), 6.65 (1H, s), 3.67 (2H, t, J=7.0 Hz), 2.99 (2H, t, J=7.0 Hz).

STEP 3. 2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethylamine

25 The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazole (step 2).

MS (EI) m/z: 405 (M⁺).

STEP 4. N-{[(2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethylamine (step 3).

¹H-NMR (CDCl₃) δ: 8.17 (1H, s), 7.69 (2H, d, J=8.4 Hz), 7.57 (1H, d, J=2.2 Hz), 7.30-7.18 (8H, m), 6.82-6.77 (1H, m), 6.60 (1H, d, J=2.2 Hz), 3.64-3.58 (2H, m), 2.91 (2H, t, J=6.4 Hz), 2.39 (3H, s).

STEP 5. N-{[(2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide mono-p-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from N-{[(2-{4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (step 4).

¹H-NMR (DMSO-d₆) δ: 10.64 (1H, br.s), 8.24 (1H, s), 8.35 (1H, s), 7.78-7.75 (3H, m), 7.49-7.80 (8H, m), 7.11 (2H, d, J=7.9 Hz), 6.60-6.57 (1H, m), 6.38-6.37 (1H, m), 3.33-3.26 (2H, m), 2.78 (2H, t, J=7.2 Hz), 2.32 (3H, s), 2.28 (3H, s).

MS (ESI) m/z: 603 [(MH)⁺], 601 [(M-H)⁻].

EXAMPLE 266

3-(3-CHLORO-4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL)PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-B]PYRIDINE

STEP 1. diethyl 2-(2-chloro-4-nitrophenyl)malonate

Diethylmalonate (5.2 ml, 34.2 mmol) was added to the suspension of NaH (1.4 g, 34.2 mmol) in 80 ml of 1,4-dioxane followed by the successive

addition of CuBr (4.9 g, 34.2 mmol) and 3-chloro-4-fluoronitrobenzene (5.0 g, 28.5 mmol). The mixture was stirred at room temperature for 0.5 h and under reflux temperature for 12 h. The mixture was poured into water, and the precipitate was filtered off through a pad of celite. The filtrate was extracted with ethyl acetate (2 x 50 ml). The organic layer was washed with brine, dried (MgSO₄), and concentrated to give a green oil. This mixture was purified by SiO₂ column chromatography developing with hexane/ethyl acetate (10/1) gave 7.6 g (85%) of the title compound as yellow oil.

¹H-NMR (CDCl₃) δ: 8.30 (1H, d, J=2.4 Hz), 8.16 (1H, dd, J=2.2, 8.6 Hz), 7.74 (1H, d, J=8.6 Hz), 5.27 (1H, s), 4.28 (2H, q, J=7.2 Hz), 4.27 (2H, q, J=7.2 Hz), 1.29 (6H, t, J=7.2 Hz).

STEP 2. 2-(2-chloro-4-nitrophenyl)acetic acid

To a solution of diethyl 2-(2-chloro-4-nitrophenyl)malonate (step 1, 7.6 g, 24.2 mmol) in methanol (18 ml) was added 6M-NaOH (12 ml) and stirred for 1 h at 50°C. The reaction was quenched by the addition of saturated citric acid aqueous solution (16 ml) and water. The organic layer was extracted with ethyl acetate (2 x 50 ml), washed with brine, dried (MgSO₄) and concentrated to give 4.52 g (87%) of title compound as light yellow solid.

¹H-NMR (CDCl₃) δ: 12.6 (1H, br.s), 8.30 (1H, d, J=2.6 Hz), 8.18 (1H, dd, J=2.4, 8.4 Hz), 7.73 (1H, d, J=8.6 Hz), 3.90 (2H, s).

STEP 3. methyl 2-(2-chloro-4-nitrophenyl)acetate

To a solution of 2-(2-chloro-4-nitrophenyl)acetic acid (step 2, 4.5 g, 21 mmol) in dimethyl acetale/methanol (4/1) was added trimethylsilylchloride (0.3 ml) and stirred for 7 h at room temprature. The solvent was removed and the residue was purified by SiO₂ column chromatography with developing hexane/ethyl acetate (10/1) to give 3.6 g (74%) of title compound as yellow oil.

¹H-NMR (CDCl₃) δ: 8.28 (1H, d, J=2.3 Hz), 8.11 (1H, dd, J=2.3, 8.6 Hz), 7.50 (1H, d, J=8.6 Hz), 3.88 (2H, s), 3.74 (3H, s).

STEP 4. methyl 2-(4-amino-2-chlorophenyl)acetate

To a solution of methyl 2-(2-chloro-4-nitrophenyl)acetate (step 3, 3.6 g, 15.6 mmol) in ethanol/water (4/1) were added Fe (4.4 g, 78.0 mmol) and NH₄Cl (409 mg, 7.8 mmol). The mixture was stirred for 1 h under reflux temperature. The solvent was removed and the residue was diluted with CH₂Cl₂. The mixture was washed with brine, dried (MgSO₄) and concentrated to give 2.59 g (83%) of title compound as orange oil.

The title compound was prepared according to the procedure described in step 2 of Example 28 from methyl 2-(2-chloro-4-nitrophenyl)acetate (step 3)

¹H-NMR (CDCl₃) δ: 7.04 (1H, d, J=8.2 Hz), 6.72 (1H, d, J=2.3 Hz), 6.54 (1H, dd, J=2.5, 8.2 Hz), 3.70 (3H, s), 3.66 (2H, s).

STEP 5. methyl 2-chloro-4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl} acetate

To a mixture of methyl 2-(4-amino-2-chlorophenyl)acetate (step 4, 2.6 g, 13.0 mmol) and 4,6-Dimethyl-3-nitro-2-pyridine (step 2 of Example 1, 2.4 g, 13.0 mmol) in DMSO was added diisopropylethylamine. The resulting mixture was stirred for 9 h at 50 °C. To the mixture was poured into water and extracted with ethyl acetate (3 x 30 ml). The organic layer was washed with brine, dried (MgSO₄) and concentrated to give a brown oil. This was purified by SiO₂ column chromatography with developing hexane/ethyl acetate (10/1) to give 1.4 g (29%) of title compound as yellow solid.

¹H-NMR (CDCl₃) δ: 9.55 (1H, br.s), 7.90 (1H, d, J=2.2 Hz), 7.43 (1H, dd, J=2.2, 8.3 Hz), 7.24 (1H, d, J=8.3 Hz), 6.59 (1H, s), 3.76 (2H, s), 3.72 (3H, s), 2.56 (3H, s), 2.46 (3H, s).

MS (EI) m/z : 349 (M^+).

STEP 6. methyl 2-chloro-4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}acetate

The title compound was prepared according to the procedure described in step 2 of Example 28 from methyl {2-chloro-4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}acetate (step 5)

$^1\text{H-NMR}$ (CDCl_3) δ : 7.26 (1H, d, $J=2.2$ Hz), 7.20 (1H, d, $J=8.3$ Hz), 7.00 (1H, dd, $J=2.2, 8.3$ Hz), 6.64 (1H, s), 6.37 (1H, br.s), 3.70 (3H, s), 3.27 (1H, br.s), 2.68 (3H, s), 2.38 (3H, s), 2.20 (3H, s).

STEP 7. methyl 2-[2-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl) phenylethyl acetate

The title compound was prepared according to the procedure described in step 5 of Example 1 from methyl 2-chloro-4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}acetate (step 6)

$^1\text{H-NMR}$ (CDCl_3) δ : 7.50 (1H, d, 8.3 Hz), 7.47 (1H, d, $J=2.2$ Hz), 7.31 (1H, dd, $J=2.2, 8.3$ Hz), 6.92 (1H, s), 3.87 (2H, s), 3.77 (3H, s), 2.85 (2H, q, $J=7.5$ Hz), 2.65 (3H, s), 2.53 (3H, s), 1.31 (3H, t, $J=7.5$ Hz).

MS (EI) m/z : 357 (M^+).

STEP 8. 2-[2-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl) phenylethanol

To a solution of methyl 2-[2-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl) phenylethyl acetate (step 7, 1.13 g, 3.15 mmol) was added carefully LAH and stirred for 1 h at room temperature. The reaction was quenched with water and the mixture was diluted with ethyl acetate (50 ml). To this mixture was added saturated potassium sodium tartarate aqueous solution (50 ml) and stirred for 2.5 h. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic layer was

washed with brine, dried (MgSO₄) and concentrated to give 1.0 g of title compound as white solid.

¹H-NMR (CDCl₃) δ: 7.41-7.53 (2H, m), 7.25-7.29 (1H, m), 6.92 (1H, s), 3.96 (2H, m), 3.11(3H, t, J=7.4 Hz), 2.82 (2H, m), 2.65 (3H, s), 2.53 (3H, s), 1.30 (3H, t, J=7.4 Hz).

MS (EI) m/z: 329 (M⁺).

STEP 9. 3-[3-chloro-4-(2-chloroethyl)phenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from methyl 2-[2-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenylethanol (step 8)

¹H-NMR (CDCl₃) δ: 7.45-7.52 (2H, m), 7.23-7.31 (1H, m), 6.92 (1H, s), 3.82 (2H, t, J=7.3 Hz), 3.29 (2H, t, J=7.3 Hz), 2.83 (2H, q, J=7.6 Hz), 2.65 (3H, s), 2.53 (3H, s), 1.30 (3H, t, J=7.6 Hz).

STEP 10. 3-[4-(2-azidoethyl)-3-chlorophenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[3-chloro-4-(2-chloroethyl)phenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (step 9)

¹H-NMR (CDCl₃) δ: 7.45-7.48 (2H, m), 7.29 (1H, dd, J=2.1, 7.9 Hz), 6.92 (1H, s), 3.62 (1H, t, J=7.1 Hz), 3.12 (1H, t, J=7.3 Hz), 2.83 (2H, q, J=7.4 Hz), 2.65 (3H, s), 2.53 (3H, s), 1.30 (3H, t, J=7.4 Hz).

STEP 11. 2-[2-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanamine

To a solution of methyl 3-[4-(2-azidoethyl)-3-chlorophenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (step 10, 430 mg, 1.2 mmol) in ethanol/water (4/1) were added Fe (335 mg, 6.0 mmol) and NH₄Cl (409 mg, 7.8

mmol). The mixture was stirred for 1 h under reflux temperature. The solvent was removed and the residue was diluted with CH_2Cl_2 . The mixture was washed with brine, dried (MgSO_4) and concentrated to give 390 mg of title compound as orange oil.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 7.44 (2H, d, $J=7.4$ Hz), 7.25 (1H, m), 6.92 (1H, s), 2.92-3.15 (6H, m), 2.83 (2H, q, $J=7.4$ Hz), 2.65 (3H, s), 2.53 (3H, s), 1.30 (3H, t, $J=7.4$ Hz).

STEP 12. 2-[2-chloro-4-(-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanamine

- 10 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[2-chloro-4-(-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanamine (Step 11)

- $^1\text{H-NMR}$ (CDCl_3) δ : 7.83 (2H, d, $J=8.4$ Hz), 7.28-7.36 (4H, m), 7.14 (1H, d, $J=7.7$ Hz), 6.92 (1H, s), 6.28 (1H, br.s), 3.58 (2H, dt, $J=6.3$ Hz), 3.02 (2H, t, $J=6.4$ Hz), 2.74 (2H, q, $J=7.6$ Hz), 2.66 (3H, s), 2.45 (3H, s), 2.41 (3H, s), 1.25 (3H, t, $J=7.6$ Hz).

MS (ESI) m/z : 526 (M^+).

EXAMPLE 267

- 20 3-(2-CHLORO-4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-B]PYRIDINE
STEP 1. 2-{3-chloro-4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol

- 25 The title compound was prepared according to the procedure described in step 3 of Example 1 from 4,6-Dimethyl-3-nitro-2-pyridine (0.66 g, 3.8 mmol, step 2 of Example 1) and 4-amino-2-chloro-phenylethanol (0.72 g, 3.8 mmol, *Eur. J. Med. Chem.*, 1996, 31, 133.).

¹H-NMR (CDCl₃) δ: 9.85 (1H, s), 8.37 (1H, d, J=8.4 Hz), 7.31 (1H, d, J=2.0 Hz), 7.14 (1H, dd, J=2.0, 8.3 Hz), 6.60 (1H, s), 3.87 (2H, dt, J=6.2, 6.4 Hz), 2.84 (2H, t, J= 6.4Hz), 2.56 (3H, s), 2.46 (3H, s), 1.40 (1H, t, J= 6.2Hz).
MS (EI) m/z: 321 (M⁺).

5 STEP 2. methyl 3-chloro-4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[3-chloro-4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl]ethanol (step 1).

10 ¹H-NMR (CDCl₃) δ: 7.26 (1H, d, J=2.2 Hz), 7.20 (1H, d, J=8.3 Hz), 7.00 (1H, dd, J=2.2, 8.3 Hz), 6.64 (1H, s), 6.37 (1H, br.s), 3.70 (3H, s), 3.27 (1H, br.s), 2.68 (3H, s), 2.38 (3H, s), 2.20 (3H, s).

STEP 3. 2-[2-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenylethyl propionate

15 The title compound was prepared according to the procedure described in step 5 of Example 1 from 3-chloro-4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethyl propionate (step 2).

¹H-NMR (CDCl₃) δ: 7.50 (1H, d, 8.3 Hz), 7.47 (1H, d, J=2.2 Hz), 7.31 (1H, dd, J=2.2, 8.3 Hz), 6.92 (1H, s), 3.87 (2H, s), 3.77 (3H, s), 2.85 (2H, q, J=7.5 Hz), 2.65 (3H, s), 2.53 (3H, s), 1.31 (3H, t, J=7.5 Hz).

MS (EI) m/z: 357 (M⁺).

STEP 4. 2-[3-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenylethanol

25 The title compound was prepared according to the procedure described in step 6 of Example 1 from methyl 2-[2-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl) phenylethyl propionate (step 3).

¹H-NMR (CDCl₃) δ: 7.51 (1H, s), 7.34 (2H, s), 6.91 (1H, s), 3.96 (2H, dd, J=6.2, 12.0 Hz), 2.96 (2H, t, J=7.4 Hz), 2.70 (2H, m), 2.66 (3H, s), 2.51 (3H, s), 1.67 (1H, br.t, J=6.2 Hz), 1.28 (3H, t, J=7.4 Hz).

MS (ESI) m/z: 329 (M⁺).

5 STEP 5. 3-[2-chloro-4-(2-chloroethyl)phenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[3-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl) phenylethanol (step 4).

10 ¹H-NMR (CDCl₃) δ: 7.49 (1H, d, J=1.3 Hz), 7.34-7.49 (2H, m), 6.91 (1H, s), 3.80 (2H, t, J=7.2 Hz), 3.17 (2H, t, J=7.0 Hz), 2.60-2.85 (2H, m), 2.66 (3H, s), 2.51 (3H, s), 1.28 (3H, t, J=7.5 Hz).

MS (EI) m/z: 347 [(M-H)].

15 STEP 6. 3-[4-(2-azidoethyl)-3-chlorophenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[2-chloro-4-(2-chloroethyl)phenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (step 5).

20 ¹H-NMR (CDCl₃) δ: 7.49 (1H, m, J=1.8 Hz), 7.31-7.38 (2H, m), 6.91 (1H, s), 3.62 (2H, t, J=7.0 Hz), 2.98 (2H, t, J=7.3 Hz), 2.60-2.80 (2H, m), 2.66 (3H, s), 2.51 (3H, s), 1.27 (3H, t, J=7.5 Hz).

MS (EI) m/z: 354 (M⁺).

STEP 7. 2-[3-chloro-4-(-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanamine

25 To a stirred solution of 3-[4-(2-azidoethyl)-3-chlorophenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (step 6, 149 mg, 0.4 mmol) in THF (4 ml) was added triphenylphosphine (116 mg, 0.4 mmol) at room temperature. After

completion of the addition, the stirring was continued for an additional 2.5 h at the same temperature and 3.5 h under reflux temperature. To the resulting mixture was added H₂O (1.0 ml) at room temperature, and the solvent was removed. The mixture was dissolved in CH₂Cl₂ (100 ml), washed with brine.

- 5 The Organic layer was dried (MgSO₄), and concentrated to give a yellow oil.
MS (EI) m/z: 328 (M⁺).

STEP 8. 2-[3-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanamine

- 10 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[3-chloro-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethanamine (step 7).

¹H-NMR (CDCl₃) δ: 7.88 (1H, s), 7.85 (1H, s), 7.19-7.34 (5H, m), 6.92 (1H, s), 6.94 (1H, s), 6.13 (1H, br.s), 3.54 (2H, m), 2.78 (2H, t, J=6.4 Hz), 2.67 (3H, s), 2.63 (3H, m), 2.42 (3H, s), 2.40 (3H, s), 1.25 (3H, t, J=7.5 Hz).

- 15 MS (EI) m/z: 526 (M⁺).

EXAMPLE 268

2-ETHYL-3-(3-METHOXY-4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-5,7-DIMETHYL-3H-IMIDAZO[4,5-B]PYRIDINE

- 20 STEP 1. diethyl 2-(2-methoxy-4-nitrophenyl)malonate

The title compound was prepared according to the procedure described in step 1 of Example 266 from 4-bromo-3-methoxynitrobenzene.

- ¹H-NMR (CDCl₃) δ: 7.78 (1H, dd, J=2.2, 8.4 Hz), 7.75 (1H, d, J=2.2 Hz), 7.54 (1H, d, J=8.4 Hz), 5.15 (1H, s), 4.25 (2H, q, J=7.2 Hz), 4.25 (2H, q, J=7.2 Hz), 3.94 (3H, s), 1.28 (6H, t, J=7.2 Hz).

STEP 2. 2-(2-methoxy-4-nitrophenyl)acetic acid

The title compound was prepared according to the procedure described in step 2 of Example 266 from diethyl 2-(2-methoxy-4-nitrophenyl)malonate (step 1).

¹H-NMR (CDCl₃) δ: 12.4 (1H, br.s), 7.82 (1H, dd, J=2.2, 8.4 Hz), 7.75 (1H, dd, J=2.2 Hz), 7.50 (1H, d, J=8.4 Hz), 3.90 (3H, s), 3.66 (2H, s).

STEP 3. methyl 2-(2-methoxy-4-nitrophenyl)acetate

To a solution of 2-(2-methoxy-4-nitrophenyl)acetic acid (step 2, 1.2 g, 5.5 mmol) in methanol/dichloromethane (11 ml, 1/1) was added trimethylsilyldiazomethane (2 M, 5.6 ml, 11.8 mmol) and stirred for 10 min at room temperature. The mixture was quenched with saturated citric acid aqueous solution and the extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with brine, dried (MgSO₄) and concentrated to give 1.2 g of title compound as orange solid.

¹H-NMR (CDCl₃) δ: 7.83 (1H, dd, J=2.2, 8.3 Hz), 7.73 (1H, dd, J=2.2 Hz), 7.34 (1H, d, J=8.1 Hz), 3.93 (3H, s), 3.71 (2H, s), 3.71 (3H, s).

STEP 4. methyl 2-(4-amino-2-methoxyphenyl)acetate

To a solution of methyl 2-(2-methoxy-4-nitrophenyl) acetate (step 3, 1.2 g, 5.5 mmol) in methanol (10 ml) was added 10% Pd/C (130 mg, 0.12 mmol) and stirred under hydrogen atmosphere for 3 h at room temperature. The catalyst was filtered off through a pad of celite and well washed with ethanol and ethyl acetate. The filtrate was concentrated to give 1.1 g of title compound as pink oil.

¹H-NMR (CDCl₃) δ: 6.94 (1H, d, J=7.7 Hz), 6.26 (1H, d, J=2.0 Hz), 6.23 (1H, s), 3.70 (3H, s), 3.76 (3H, s), 3.67 (3H, s), 3.52 (2H, s).

STEP 5. methyl {4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]-2-methoxyphenyl}acetate

The title compound was prepared according to the procedure described in step 3 of Example 1 from methyl 2-(4-amino-2-methoxyphenyl) acetate (step 4).

¹H-NMR (CDCl₃) δ: 9.60 (1H, s), 7.47 (1H, d, J=1.7 Hz), 7.06-7.15 (2H, m), 6.55 (1H, s), 3.84 (3H, s), 3.69 (3H, s), 3.62 (2H, s), 2.56 (3H, s), 2.44 (3H, s). MS (EI) m/z: 345 (M⁺).

STEP 6. methyl {4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]-2-methoxyphenyl}acetate

The title compound was prepared according to the procedure described in step 2 of Example 28 from methyl {4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]-2-methoxyphenyl}acetate (step 5).

¹H-NMR (CDCl₃) δ: 7.03 (1H, d, J=5.1 Hz), 7.02 (1H, s), 6.60 (1H, s), 6.57 (1H, dd, J=2.2, 8.3 Hz), 3.79 (3H, s), 3.68 (3H, s), 3.56 (2H, s), 3.25-3.35(br.s, 2H), 2.38 (3H, s), 2.20 (3H, s).

MS (EI) m/z: 315 (M⁺).

STEP 7. methyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)-2-methoxyphenyl]ethyl acetate

The title compound was prepared according to the procedure described in step 5 of Example 1 from methyl {4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]-2-methoxyphenyl}acetate (step 6).

¹H-NMR (CDCl₃) δ: 7.36 (1H, d, J=7.9 Hz), 6.89-6.99 (3H, m), 3.84 (2H, s), 3.74 (3H, s), 3.71 (2H, s), 2.85 (2H, q, J=7.5 Hz), 2.66 (3H, s), 2.53 (3H, s), 1.30 (3H, t, J=7.5 Hz).

MS (EI) m/z: 353 (M⁺).

STEP 8. 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)-2-methoxyphenyl]ethanol

The title compound was prepared according to the procedure described in step 8 of Example 266 from methyl 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methoxyphenylethyl acetate (step 7).

¹H-NMR (CDCl₃) δ: 7.33 (1H, d, J=7.7 Hz), 6.87-6.95 (3H, m), 3.90 (2H, dt, J=6.0, 6.2 Hz), 3.84 (3H, s), 2.98(2H, t, J=6.4 Hz), 2.84(2H, q, J=7.5 Hz), 2.66 (3H, s), 2.53 (3H, s), 1.76 (1H, br.t), 1.30 (3H, t, J=7.5 Hz).

MS (EI) m/z: 324 [(M-H)].

STEP 9. 3-[4-(2-chloroethyl)-3-methoxyphenyl-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methoxyphenylethanol (step 8).

¹H-NMR (CDCl₃) δ: 7.33 (1H, d, J=7.7 Hz), 6.87-6.94 (3H, m), 3.84 (3H, s), 3.77 (3H, t, J=7.6 Hz), 3.16 (2H, t, J=7.3 Hz), 2.84 (2H, q, J=7.6 Hz), 2.66 (3H, s), 2.53 (3H, s), 1.30 (3H, t, J=7.6 Hz).

STEP 10. 3-[4-(2-azidoethyl)-3-methoxyphenyl-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[4-(2-chloroethyl)-3-methoxyphenyl-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (step 9).

¹H-NMR (CDCl₃) δ: 7.45-7.48 (2H, m), 7.29 (1H, dd, J=2.1, 7.9 Hz), 6.92 (1H, s), 3.62 (1H, t, J=7.1 Hz), 3.12 (1H, t, J=7.3 Hz), 2.83 (2H, q, J=7.4 Hz), 2.65 (3H, s), 2.53 (3H, s), 1.30 (3H, t, J=7.4 Hz).

STEP 11. 2-[4-(-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl-2-methoxy)phenyl]ethanamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 3-[4-(2-azidoethyl)-3-methoxyphenyl]-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (step 10).

¹H-NMR (CDCl₃) δ: 7.30 (1H, d, J=7.7 Hz), 6.92 (1H, dd, J=2.0, 7.9 Hz), 6.91 (1H, br.s), 6.86 (1H, d, J=2.0 Hz), 3.83 (3H, s), 2.65 (3H, s), 2.99 (2H, br.t, J=4.5 Hz), 2.85 (2H, q, J=8.3 Hz), 2.84 (2H, q, J=7.7 Hz), 2.66 (3H, s), 2.53 (3H, s), 1.29 (3H, t, J=7.7 Hz).

STEP 12. 2-ethyl-(3-methoxy-4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl-2-methoxy)phenyl] ethanamine (step 11).

¹H-NMR (CDCl₃) δ: 7.86 (2H, d, J=8.3 Hz), 7.30 (4H, m), 7.14 (1H, d, J=8.1 Hz), 7.01 (1H, d, J=7.9 Hz), 6.92 (1H, s), 6.79 (1H, d, J=2.0 Hz), 6.63 (1H, dd, J=1.8, 7.7 Hz), 6.04 (1H, br.t, J=5.1 Hz), 3.74 (3H, s), 3.51 (2H, dt, J=6.0 Hz), 2.85 (2H, t, J=6.2 Hz), 2.70 (2H, q, J=7.5 Hz), 2.66 (3H, s), 2.44 (3H, s), 2.41 (3H, s), 1.23 (3H, t, J=7.5 Hz).

MS (ESI) *m/z*: 522 [(M+H)⁺], 520 [(M-H)⁻].

EXAMPLE 269

2-ETHYL-3-(3-METHYL-4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-5,7-DIMETHYL-3*H*-IMIDAZO[4,5-*B*]PYRIDINE
STEP 1. diethyl 2-(2-methyl-4-nitrophenyl)malonate

The title compound was prepared according to the procedure described in step 1 of Example 268 from 4-bromo-3-methylnitrobenzene.

¹H-NMR (CDCl₃) δ: 8.10 (1H, s), 8.05-8.10 (1H, m), 7.62 (1H, d, J=9.2 Hz), 4.93 (1H, s), 4.26 (2H, q, J=7.3 Hz), 4.25 (2H, q, J=7.3Hz), 2.46 (3H, s), 1.28 (6H, t, J=7.3 Hz).

STEP 2. 2-(2-methyl-4-nitrophenyl)acetic acid

- 5 The title compound was prepared according to the procedure described in step 2 of Example 266 from diethyl 2-(2-methyl-4-nitrophenyl) malonate (step 1)

¹H-NMR (CDCl₃) δ: 8.08 (1H, br.s), 8.02 (1H, dd, J=8.6 Hz), 7.49 (1H, d, J=8.4 Hz), 3.77 (2H, s), 2.35 (3H, s).

10 STEP 3. methyl 2-(2-methyl-4-nitrophenyl)acetate

The title compound was prepared according to the procedure described in step 3 of Example 266 from 2-(2-methyl-4-nitrophenyl)acetic acid (step 2).

¹H-NMR (CDCl₃) δ: 8.07 (1H, d, J=2.1 Hz), 8.02 (1H, dd, J=2.3, 5.9 Hz), 7.36 (1H, d, J=8.4 Hz), 3.74 (2H, s), 3.71 (3H, s), 2.42 (3H, s).

15 STEP 4. methyl 2-(4-amino-2-methylphenyl)acetate

The title compound was prepared according to the procedure described in step 4 of Example 268 from methyl 2-(2-methyl-4-nitrophenyl)acetate (step 3)

¹H-NMR (CDCl₃) δ: 6.97 (1H, d, J=7.9 Hz), 6.48-6.52 (2H,m), 3.67 (3H, s), 3.57 (2H, br.s), 3.53 (3H, s), 2.22 (3H, s).

20 STEP 5. methyl {4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]-2-methylphenyl}acetate

The title compound was prepared according to the procedure described in step 3 of Example 1 from methyl 2-(4-amino-2-methylphenyl) acetate (step 4).

¹H-NMR (CDCl₃) δ: 7.54 (1H, br.d, J=8.3 Hz), 7.38 (1H, br.s), 7.17 (1H, d, J=8.39 Hz), 6.52 (1H, s), 3.69 (3H, s), 3.63 (2H, s), 2.55 (3H, s), 2.43 (3H, s), 2.32 (3H, s).

MS (EI) m/z: 345 (M⁺).

5 STEP 6. methyl {4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]-2-methylphenyl}acetate

The title compound was prepared according to the procedure described in step 2 of Example 28 from methyl {4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]-2-methylphenyl}acetate (step 5).

10 ¹H-NMR (CDCl₃) δ: 7.07 (1H, d, J=9.0 Hz), 6.91-6.93 (2H, m), 6.62 (1H, s), 6.36 (1H, br.s), 3.79 (3H, s), 3.67 (3H, s), 3.57 (2H, s), 3.30 (br.s, 2H), 2.37 (3H, s), 2.26 (3H, s), 2.2 (3H, s).

STEP 7. methyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylphenylethyl acetate

15 The title compound was prepared according to the procedure described in step 5 of Example 1 from methyl {4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]-2-methylphenyl}acetate (step 6).

¹H-NMR (CDCl₃) δ: 7.39 (1H, d, J=7.6 Hz), 7.17-7.25 (2H, m), 6.90 (1H, s), 3.74 (3H, s), 3.72 (2H, s), 2.82 (2H, q, J=7.4 Hz), 2.65 (3H, s), 2.52 (3H, s), 2.40 (3H, s), 1.28 (3H, t, J=7.6 Hz).

MS (EI) m/z: 337 (M⁺).

STEP 8. 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylphenylethanol

25 The title compound was prepared according to the procedure described in step 8 of Example 266 from methyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylphenylethyl acetate (step 7).

¹H-NMR (CDCl₃) δ: 7.35 (1H, d, J=7.9 Hz), 7.17 (1H, s), 7.16 (1H, d, J=7.9 Hz), 6.90 (1H, s), 3.84 (2H, dt, J=6.8 Hz), 2.96 (2H, t, J=7.0 Hz), 2.81 (2H, q, J=7.5 Hz), 2.66 (3H, s), 2.52 (3H, s), 2.40 (s, 3H), 1.91 (1H, br.t), 1.28 (3H, t, J=7.5 Hz).

5 MS (EI) m/z: 324 [(M-H)].

STEP 9. 3-[4-(2-chloroethyl)-3-methylphenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylphenylethanol (step 8).

¹H-NMR (CDCl₃) δ: 7.35 (1H, d, J=8.4 Hz), 7.17-7.19 (2H, m), 6.90 (1H, s), 3.75 (2H, t, J=7.6 Hz), 3.17 (2H, t, J=7.6 Hz), 2.81 (2H, q, J=7.5 Hz), 2.65 (3H, s), 2.41 (3H, s), 2.36 (3H, s), 1.28 (3H, t, J=7.5 Hz).

STEP 10. 3-[4-(2-azidoethyl)-3-methylphenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 8 of Example 1 from 3-[4-(2-chloroethyl)-3-methylphenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (step 9).

¹H-NMR (CDCl₃) δ: 7.34 (1H, d, J=8.7 Hz), 7.19-7.26 (2H, m), 6.90 (1H, s), 3.62 (1H, t, J=7.1 Hz), 3.56 (2H, t, J=7.6 Hz), 2.99 (2H, t, J=7.6 Hz), 2.81 (2H, q, J=7.6 Hz), 2.65 (3H, s), 2.52 (3H, s), 2.41 (3H, s), 1.27 (3H, t, J=7.6 Hz).

STEP 11. 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylphenyl]ethanamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 3-[4-(2-azidoethyl)-3-methylphenyl-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (step 10).

¹H-NMR (CDCl₃) δ: 7.32 (1H, d, J=7.7 Hz), 7.14-7.16 (2H, m), 6.91 (1H, br.s), 6.90 (1H, s), 3.02 (2H, br.t, J=7.3 Hz), 2.77-2.87 (4H, m), 2.65 (3H, s), 2.53 (3H, s), 2.40 (3H, s), 1.28 (3H, t, J=7.5 Hz).

STEP 12. 2-ethyl-(3-methyl-4-{2-[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-[4-(-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl-2-methyl)phenyl]ethanamine (step 11).

¹H-NMR (CDCl₃) δ: 7.86 (1H, d, J=8.0 Hz), 7.31 (1H, d, J=8.0 Hz), 7.03 (1H, d, J=7.9 Hz), 6.91 (1H, s), 6.85 (1H, d, J=8.4 Hz), 6.07-6.11 (1H, m), 3.51 (2H, q, J=6.4 Hz), 2.85 (2H, t, J=6.4 Hz), 2.61-2.69 (2H, m), 2.69 (3H, s), 2.44 (3H, s), 2.28 (3H, s), 1.23 (3H, t, J=7.5 Hz).

MS (ESI) m/z: 506 [(M+H)⁺], 504 [(M-H)⁻].

EXAMPLE 270

6-CHLORO-2-ETHYL-1-(6-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL)-3-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOLE

STEP 1. (4-amino-2-pyridinyl)acetonitrile

The title compound was prepared according to the procedure described in step 2 of Example 28 from (4-nitro-2-pyridinyl)acetonitrile (8.6 g, 52.9 mmol, Katz; R. B.; Voyle, M., *Synthesis.*, 1989, 4, 314.).

¹H-NMR (CDCl₃) δ: 8.04 (1H, d, J=2.8 Hz), 7.17 (1H, d, J=8.2 Hz), 6.99 (1H, dd, J=2.8, 8.4 Hz), 3.81 (2H, s), 3.76 (2H, br.s).

STEP 2. {5-[5-chloro-2-nitro-4-(trifluoromethyl)anilino]-2-pyridinyl}acetonitrile

The title compound was prepared according to the procedure described in step 3 of Example 1 from (5-aminopyridine-2-yl)acetonitrile (step 1).

¹H-NMR (CDCl₃) δ: 9.66 (1H, s), 8.60 (2H, m), 7.71 (1H, dd, J=2.6, 8.4 Hz), 7.60 (1H, d, J=8.3 Hz), 7.13 (1H, s), 4.03 (2H, s)
MS (EI) m/z: 356 (M⁺).

STEP 3. {5-[2-amino-5-chloro-4-(trifluoromethyl)anilino]-2-

pyridinyl} acetonitrile

The title compound was prepared according to the procedure described in step 2 of Example 28 from {5-[5-chloro-2-nitro-4-(trifluoromethyl)anilino]-2-pyridinyl} acetonitrile (step 2).

¹H-NMR (CDCl₃) δ: 8.25 (1H, d, J=2.1 Hz), 7.12-7.34 (3H, m), 5.47 (1H, br.s), 3.89 (2H, s), 3.78 (2H, br.s).

STEP 4. {5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-

pyridinyl} acetonitrile

The title compound was prepared according to the procedure described in step 5 of Example 1 from {5-[2-amino-5-chloro-4-(trifluoromethyl)anilino]-2-pyridinyl} acetonitrile (step 3).

¹H-NMR (CDCl₃) δ: 8.66 (1H, s), 8.15 (1H, s), 7.73-7.83 (2H, m), 7.12 (1H, s), 4.12 (2H, s), 2.79 (2H, q, J=7.6 Hz), 1.40 (3H, t, J=7.6 Hz).

STEP 5. 2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-

pyridinyl} ethanamine

To a solution of {5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-pyridinyl} acetonitrile (step 4, 1.0 g, 2.8 mmol), in ammonia-ethanol (30 ml) was added *Raney*-Ni and stirred for 8 h under hydrogen atmosphere (3.0 kgf/cm²). The catalyst was filtered off and the solvent was removed. The residue was diluted with ethyl acetate, washed with brine, dried (MgSO₄) and concentrated to give 813 mg of title compound as black solid.

MS (EI) m/z: 368 (M⁺).

STEP 6. 6-chloro-2-ethyl-1-(6-{2-
[({[(4methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}-3-pyridinyl)-5-
(trifluoromethyl)-1H-benzimidazol

The title compound was prepared according to the procedure described
5 in step 10 of Example 1 from 2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-
benzimidazol-1-yl]-2-pyridinyl}ethanamine (step 5).

¹H-NMR (CDCl₃) δ: 8.63 (1H, d, J=2.2 Hz), 8.14 (1H, s), 7.77 (2H, d, J=8.3
Hz), 7.66 (1H, dd, J=2.6, 8.3 Hz), 7.45 (1H, d, J=8.3 Hz), 7.30 (2H, d, J=8.4 Hz),
7.21 (1H, s), 3.73-3.80 (2H, m), 3.17 (2H, t, J=6.2 Hz), 2.79 (2H, q, J=7.5 Hz),
10 2.42 (3H, s), 1.38 (3H, t, J=7.5 Hz).

MS (ESI) m/z: 566 [(M+H)⁺], 564 [(M-H)].

EXAMPLE 271

6-CHLORO-2-ETHYL-1-(6-{2-[({[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}-3-
15 PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOLE
SODIUMSALT

The title compound was prepared according to the procedure described
in Example 2 from 6-chloro-2-ethyl-1-(6-{2-
[({[(4methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}-3-pyridinyl)-5-
20 (trifluoromethyl)-1H-benzimidazol (Example 270).

¹H-NMR (DMSO-d₆) δ: 8.71 (1H, br.s), 8.20 (1H, br.s), 7.95 (1H, m), 7.43-7.64
(4H, m), 7.12 (2H, br.s), 6.09 (1H, br.s), 3.39 (2H, br.s), 2.92 (2H, br.s), 2.73
(2H, br.s), 2.28 (3H, br.s), 1.27 (3H, br.s).

MS (ESI) m/z: 566 [(M+H)⁺], 564 [(M-H)].

25 EXAMPLE 272

2-{5-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]-2-PYRIDINYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1.ethyl(5-amino-2-pyridinyl)acetate

To a solution of (5-amino-2-pyridinyl)acetic acid (1.46 g, 9.6 mmol, Daisley; R. W.; Hanbali, J. R., *Synthetic Communications.*, 1981, 11(9), 743.) in ethanol was added conc. H₂SO₄ and stirred for 16.5 h under hydrogen atmosphere at room temperature. The mixture was neutralized with saturated NaHCO₃ aqueous solution and the solvent was removed. The mixture was diluted with water and extracted with ethyl acetate (5 x 20 ml). The organic layer was washed with brine, dried (MgSO₄) and concentrated to give 1.2 g of title compound as brown oil.

¹H-NMR (CDCl₃) δ: 8.04 (1H, d, J=2.8 Hz), 7.07 (1H, d, J=8.2 Hz), 6.96 (1H, dd, J=2.6, 8.2 Hz), 4.71 (2H, q, J=7.1 Hz), 3.72 (2H, s), 3.66 (2H, br.s), 1.25 (3H, t, J=7.1 Hz).

STEP 2. Ethyl {5-[5-chloro-2-nitro4-(trifluoromethyl)anilino]-2-pyridinyl}acetate

The title compound was prepared according to the procedure described in step 3 of Example 1 from ethyl (5-amino-2-pyridinyl)acetate (step1).

¹H-NMR (CDCl₃) δ: 9.66 (1H, s), 8.60 (2H,m), 7.71 (1H, dd, J=2.6, 8.4 Hz), 7.60 (1H, d, J=8.3 Hz), 7.13 (1H, s), 4.03 (2H, s)
MS (EI) m/z: 356 (M⁺).

STEP 3. ethyl {5-[2-amino-5-chloro-4- (trifluoromethyl)anilino]-2-pyridinyl}acetate

The title compound was prepared according to the procedure described in step 2 of Example 28 from ethyl {5-[5-chloro-2-nitro4-(trifluoromethyl)anilino]-2-pyridinyl}acetate (step2).

¹H-NMR (CDCl₃) δ: 7.25 (1H, d, J=1.5 Hz), 7.21 (1H, m), 7.16 (1H, s), 7.09 (1H, s), 7.47 (1H, d, J=8.2 Hz), 5.47 (1H, s), 4.20 (2H, q, J=7.2 Hz), 3.80 (2H, s), 3.77 (2H, br.s), 1.28 (3H, t, J=7.2 Hz).

STEP 4. ethyl {5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-pyridinyl}acetate

The title compound was prepared according to the procedure described in step 5 of Example 1 from ethyl {5-[2-amino-5-chloro-4-(trifluoromethyl)anilino]-2-pyridinyl}acetate (step 3).

¹H-NMR (CDCl₃) δ: 8.61 (1H, d, J=2.0 Hz), 8.14 (1H, s), 7.71 (1H, dd, J=2.0, 8.2 Hz), 7.62 (1H, d, J=8.2 Hz), 7.21 (1H, s), 4.27 (1H, q, J=7.3 Hz), 4.01 (2H, s), 2.79 (2H, q, J=7.6 Hz), 1.38 (3H, t, J=7.4 Hz), 1.33 (3H, t, J=7.1 Hz).

STEP 5. 2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-pyridinyl}ethanol

The title compound was prepared according to the procedure described in step 8 of Example 266 from ethyl {5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-pyridinyl}acetate (step 4).

¹H-NMR (CDCl₃) δ: 8.57 (1H, d, J=2.50 Hz), 8.13 (1H, s), 7.67 (1H, dd, J=2.6, 8.2 Hz), 7.49 (1H, d, J=8.2 Hz), 7.20 (1H, s), 4.15 (1H, q, J=5.6 Hz), 3.20 (2H, t, J=5.4 Hz), 2.79 (2H, q, J=7.4 Hz), 1.39 (3H, t, J=7.6 Hz).

STEP 6. 2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-pyridinyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-pyridinyl}ethanol (step 5).

¹H-NMR (CDCl₃) δ: 8.59 (1H, d, J=2.3 Hz), 8.13 (1H, s), 7.88 (2H, d, J=8.4 Hz), 7.65 (1H, dd, J=2.5, 8.2 Hz), 7.44 (1H, d, J=8.1 Hz), 7.32 (2H, d, J=8.1 Hz),

7.20(1H, s), 4.57 (2H, t, J=6.4 Hz), 3.25 (2H, t, J=6.6 Hz), 2.79 (2H, q, J=7.4 Hz), 2.42 (3H, s), 1.38 (3H, t, J=7.4 Hz).

MS (ESI) m/z: 567 [(M+H)⁺].

EXAMPLE 273

5 2-{5-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]-2-PYRIDINYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE HYDROCHLORIDE

The title compound was prepared according to the procedure described in Example 240 from 2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-

10 benzimidazol-1-yl]-2-pyridinyl}ethyl (4-methylphenyl)sulfonylcarbamate (Example 273).

¹H-NMR (DMSO-d₆) δ: 11.9 (1H, br.s), 8.72 (1H, br.s), 8.18 (1H, s), 8.03-8.07 (1H, m), 7.74 (1H, d, J=7.6 Hz), 7.58 (1H, d, J=8.2 Hz), 7.43 (2H, d, J=5.1 Hz), 7.39(1H, s), 4.45 (2H, t, J=6.2 Hz), 3.17 (2H, t, J=6.2 Hz), 2.76 (2H, q, J=7.6

15 Hz), 2.35 (3H, s), 1.27 (3H, t, J=7.3 Hz).

MS (ESI) m/z: 567 [(M+H)⁺], 565 [(M-H)⁻].

EXAMPLE 274

20 2-ETHYL-3-(4-{2-[(4-PYRIDINYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE

The title compound was prepared according to the procedure described in step 2 of Example 18 from phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-

imidazo[4,5-b]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 18) and pyridinyl-4-sulfonamide (Chern, Ji-Wang; Leu, Yu-Ling; et al., *J. Med. Chem.*,

25 1997, 40, 2276.; Graham, Samuel L.; Shepard, Kenneth L.; et al., *J. Med. Chem.*, 1989, 32, 2548).

m.p.: 227.9-228.7 °C.

¹H-NMR (CDCl₃) δ: 8.63 (2H, d, J=5.9 Hz), 7.65 (2H, d, J=5.9 Hz), 7.36 (4H, s), 6.96 (1H, s), 3.20 (2H, br.s), 2.75(br.s, 2H), 2.70 (2H, q, J=7.6 Hz), 2.53 (2H, s), 2.40 (3H, s), 1.20 (3H, t, J=7.6 Hz).

MS (ESI) m/z: 479 [(M+H)⁺], 477 [(M-H)].

5 EXAMPLE 275

2-ETHYL-3-(4-{2-[(2-PYRIDINYLSULFONYL)AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE

The title compound was prepared according to the procedure described in step 2 of Example 18 from phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 18) and pyridinyl-2-sulfonamide (Chern, Ji-Wang; Leu, Yu-Ling; et al., *J. Med. Chem.*, 1997, 40, 2276.; Graham, Samuel L.; Shepard, Kenneth L.; et al., *J. Med. Chem.*, 1989, 32, 2548).

¹H-NMR (CDCl₃) δ: 8.51 (1H, br.s), 8.08 (1H, br.s), 7.94 (1H, br.s), 7.29 (2H, s), 7.19 (1H, br.s), 6.91 (1H, s), 2.81 (2H, br.s), 2.73 (2H, q, J=7.6 Hz), 2.66 (3H, s), 2.78 (3H, s), 2.49(m, 2H), 1.26 (3H, t, J=7.3 Hz).

MS (ESI) m/z: 479 [(M+H)⁺], 477 [(M-H)].

EXAMPLE 276

2-ETHYL-3-(4-{2-[(3-PYRIDINYLSULFONYL)AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDINE

The title compound was prepared according to the procedure described in step 2 of Example 18 from phenyl 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethylcarbamate (step 1 of Example 18) and pyridinyl-3-sulfonamide (Chern, Ji-Wang; Leu, Yu-Ling; et al., *J. Med. Chem.*,

1997, 40, 2276.; Graham, Samuel L.; Shepard, Kenneth L.; et al., *J. Med. Chem.*, 1989, 32, 2548).

¹H-NMR (CDCl₃) δ: 9.15 (1H, d, J=1.9 Hz), 8.83 (1H, dd, J=1.9, 5.1 Hz), 8.34 (1H, dd, J=6.5 Hz), 7.50 (1H, dd, J=4.9, 8.1 Hz), 7.12-7.23 (4H, m), 6.93 (1H, s), 5.92 (1H, br.s), 3.51 (2H, q, J=5.9 Hz), 2.86 (2H, m), 2.69 (3H, m), 2.66 (3H, s), 2.43(3H, s), 1.27 (3H, t, J=7.6 Hz).

MS (ESI) m/z: 479 [(M+H)⁺]

EXAMPLE 277

2-[4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]-2-PHENYL]ETHYL-(2-CHLOROPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in step 2 of Example 243 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl} ethyl phenyl carbonate and 2-chlorophenylsulfonamide.

¹H-NMR (CDCl₃) δ: 8.18 (1H, s), 8.07 (1H, d, J=7.8Hz), 7.69 (1H, d, J=3.8Hz), 7.59 (1H, dd, J=4.3, 8.1Hz), 7.51 (2H, d, J=8.4Hz), 7.44 (2H, d, J=8.4Hz), 7.31 (1H, s), 4.29 (2H, t, J=6.2Hz), 2.94 (2H, t, J=6.5Hz), 2.76 (2H, q, J=7.6Hz), 1.26 (3H, t, J=7.3Hz)

m.p. 202.4-202.8 °C

MS (ESI) m/z: 586 [(M+H)⁺], 584 [(M-H)⁻]

EXAMPLE 278

2-[4-(2-ETHYL-5,7-DIMETHYL-3H-IMIDAZO[4,5-b]PYRIDIN-3-YL)PHENYL]-1,1-DIMETHYLETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-methyl-1-(4-nitrophenyl)-2-propanol

To a solution of 1,1-dimethyl-2-(4-nitrophenyl)ethyl acetate (52 mmol) in MeOH (50 ml) was added 4N-LiOH (40 ml) and the mixture was stirred at 50 °C for 2 h. After the solvent was removed, this mixture was diluted with water

and extracted with EtOAc (4 x 50ml). The organic layer was washed with brine, dried (MgSO₄) and concentrated. This crude was purified by SiO₂ column chromatography developing with hexane/ethyl acetate (5/1) to give the title compound as yellow oil (3.3 g, 33%).

¹H-NMR (CDCl₃) δ: 8.17 (2H, d, J=8.9Hz), 7.40 (2H, d, J=8.6Hz), 2.88 (2H, s), 1.63 (1H, br.s), 1.25 (6H, s)

STEP 2. 1-(4-aminophenyl)-2-methyl-2-propanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-methyl-1-(4-nitrophenyl)-2-propanol (step1).

¹H-NMR (CDCl₃) δ: 7.00 (2H, d, J=8.4Hz), 6.65 (2H, d, J=8.4Hz), 3.61 (2H, br.s), 2.65 (2H, s), 1.39 (1H, br.s), 1.20 (6H, s)

STEP 3. 1-{4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}-2-methyl-2-propanol

The title compound was prepared according to the procedure described in step 5 of Example 266 from 1-(4-aminophenyl)-2-methyl-2-propanol (step2)

¹H-NMR (CDCl₃) δ: 9.60 (1H, s), 7.59 (2H, d, J=8.7 Hz), 7.19 (2H, d, J=8.4Hz), 6.52 (1H, s), 2.75 (2H, s), 2.54 (3H, s), 2.43 (3H, s), 1.24 (6H, s)

STEP 4. 1-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}-2-methyl-2-propanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 1-{4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}-2-methyl-2-propanol (step3)

¹H-NMR (CDCl₃) δ: 7.10 (4H, s), 6.61 (1H, s), 6.33 (2H, s), 3.28 (1H, br.s), 2.70 (2H, s), 2.37 (3H, s), 2.20 (3H, s), 1.22 (6H, s)

STEP 5. 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-2-methyl-2-propanol

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}-2-methyl-2-propanol (step 4).

¹H-NMR (CDCl₃) δ: 7.42 (2H, d, J=8.1 Hz), 7.33 (2H, d, J=8.47 Hz), 6.91 (1H, s), 2.87 (2H, s), 2.84 (2H, q, J=7.6 Hz), 2.66 (3H, s), 2.52 (3H, s), 1.31 (6H, s), 1.28 (2H, d, J=7.6 Hz)

STEP 6. 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1,1-dimethylethyl(4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-2-methyl-2-propanol (step 5).

¹H-NMR (CDCl₃) δ: 7.94 (2H, t, J=8.6Hz), 7.33 (2H, d, J=8.6 Hz), 7.16 (4H, m), 6.93 (1H, s), 3.10 (2H, s), 2.81 (2H, q, J=7.6Hz), 2.67 (3H, s), 2.54 (3H, s), 2.40 (3H, s), 2.42 (3H, s), 1.48 (6H, s), 1.28 (3H, t, J=7.6Hz)

m.p. 173.5-174.0 °C

MS (ESI) m/z: 521 [(M+H)⁺], 519 [(M-H)⁻]

EXAMPLE 279

6-CHLORO-2-ETHYL-1-(6-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL)-3-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOLE

STEP 1. (6-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}-3-pyridinyl)methanol

The title compound was prepared according to the procedure described in step 5 of Example 266 from 1-(6-amino-3-pyridinyl)methanol.

¹H-NMR (CDCl₃) δ: 10.51 (1H, br.s), 9.26 (1H, s), 8.60 (1H, s), 8.42 (1H, s), 7.79 (1H, d, J=8.1 Hz), 7.01 (1H, d, J=8.1Hz), 4.75 (2H, s).

STEP 2. (6-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}-3-pyridinyl) methanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from {5-[5-chloro-2-nitro-4-(trifluoromethyl)anilino]-3-pyridinyl} methanol (step 1).

MS (EI) m/z: 317 (M^+).

STEP 3. {6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-3-pyridinyl} methyl proionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from (6-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}-3-pyridinyl) methanol.(Step 2).

MS (EI) m/z: 411 (M^+).

STEP 4 {6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-3-pyridinyl} methanol;

The title compound was prepared according to the procedure described in step 6 of Example 1 from {5-[5-chloro-2-nitro4-(trifluoromethyl)anilino]-3-pyridinyl} methyl propionate (step 3).

$^1\text{H-NMR}$ (CDCl_3) δ : 8.67 (1H, s), 8.19 (1H, s), 8.09 (1H, d, $J=8.6$ Hz), 7.79 (1H, d, $J=8.4$ Hz), 7.65 (1H, s), 5.54 (1H, t, $J=5.6$ Hz), 4.69 (2H, d, $J=5.6$ Hz), 2.95 (2H, q, $J=7.3$ Hz), 1.27 (3H, t, $J=7.2$ Hz).

STEP 5 6-chloro-1-[5-(chloromethyl)-2-pyridinyl]-2-ethyl-5-(trifluoromethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from {5-[5-chloro-2-nitro4-(trifluoromethyl)anilino]-3-pyridinyl} mehtanol (step 4).

¹H-NMR (CDCl₃) δ: 8.72 (1H, d, J=2.2 Hz), 8.12 (1H, s), 8.07 (1H, dd, J=2.2, 8.1 Hz), 7.45-7.48 (2H, m), 4.72 (2H, s), 3.01 (2H, q, J=7.6 Hz), 1.39 (3H, t, J=7.6 Hz).

STEP 6 {6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-yl]-3-pyridinyl} acetonitrile

To a solution of 6-chloro-1-[5-(chloromethyl)-2-pyridinyl]-2-ethyl-5-(trifluoromethyl)-1H-benzimidazole (from step 5, 550 mg, 1.5 mmol) in DMF (5 ml) and water (1 ml) was added KCN (470 g, 7.2 mmol) at room temperature, and then the reaction mixture was stirred for 2h. The mixture was diluted with water and extracted with ethyl acetate/toluene (4/1) solution (3 x 30 ml). The organic layer was washed with water, dried (MgSO₄) and concentrated. This was purified by SiO₂ column chromatography developing with hexane/ethyl acetate (1/) gave 198 mg (37%) of title compound as orange oil.

¹H-NMR (CDCl₃) δ: 8.70 (1H, d, J=2.6 Hz), 8.13 (1H, s), 8.06 (1H, dd, J=2.6, 8.0 Hz), 7.52 (1H, d, J=8.20 Hz), 7.47 (1H, s), 3.94 (2H, s), 3.01 (2H, q, J=7.5 Hz), 1.40 (3H, t, J=7.5 Hz)

STEP 7 2-{6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-yl]-3-pyridinyl} ethanamine

The title compound was prepared according to the procedure described in step 5 of Example 270 from {6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-yl]-3-pyridinyl} acetonitrile (step 6).

MS (EI) m/z: 368 (M⁺).

STEP 8 6-chloro-2-ethyl-1-(6-{2-[[{[(4methylphenyl)sulfonyl]amino}carbonyl]amino]ethyl}-2-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-3-pyridinyl} ethanamine (step 7).

¹H-NMR (CDCl₃) δ: 8.50 (1H, s), 8.12 (1H, s), 7.817 (1H, d, J=6.0 Hz), 7.72 (2H, d, J=8.4 Hz), 7.42 (1H, s), 7.24-7.37 (3H, m), 7.21 (1H, s), 6.77 (1, br.s), 3.60 (2H, dt, J=6.2 Hz), 2.94-3.01 (4H, m), 2.37 (3H, s), 1.37 (3H, t, J=7.5 Hz). MS (ESI) m/z: 566 [(M+H)⁺], 564 [(M-H)⁻].

EXAMPLE 280

2-{4-[5-CHORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-
YL]PHENYL}-1,1-DIMETHYLETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 1-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-
methyl-2-propanol

The title compound was prepared according to the procedure described in step 5 of Example 266 from 1-(4-aminophenyl)-2-methyl-2-propanol

¹H-NMR (CDCl₃) δ: 9.70 (1H, br.s), 8.58 (1H, s), 7.36 (2H, d, J=8.4Hz), 7.21-7.25 (3H, m), 2.83 (2H, s), 1.28 (6H, s)

MS (EI) m/z: 388 (M⁺)

STEP 2. 1-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-
methyl-2-propanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 1-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-methyl-2-propanol (step1)

¹H-NMR (CDCl₃) δ: 7.10 (4H, s), 6.61 (1H, s), 6.33 (2H, s), 3.28 (1H, br.s), 2.70 (2H, s), 2.37 (3H, s), 2.20 (3H, s), 1.22 (6H, s)

MS (EI) 388 (M⁺)

STEP 3. 1-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-
yl]phenyl}-2-methyl-2-propanol

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-(4- {[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)-2-methyl-2-propanol (step 2).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.48 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 7.22 (1H, s), 2.90 (2H, s), 2.80 (2H, q, J=7.3 Hz), 1.36 (3H, t, J=7.3 Hz) 1.32 (6H, s)

MS (EI) m/z: 396 (M⁺)

STEP 4. 2-{4-[5-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1,1-dimethylethyl(4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-2-methyl-2-propanol (step 3).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.94 (2H, d, J=8.7Hz), 7.36 (2H, d, J=8.1 Hz), 7.15-7.27 (5H, m), 3.16 (2H, s), 2.78 (2H, q, J=7.6Hz), 2.43 (3H, s), 1.47 (6H, s), 1.37 (3H, t, J=7.6Hz)

m.p. 174.6-175.3 °C

MS (ESI) m/z: 594 [(M+H)⁺], 592 [(M-H)⁻]

EXAMPLE 281

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(2,4-DIMETHYL-1,3-THIAZOL-5-YL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in step 2 of Example 243 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl phenyl carbonate and 2,4-dimethyl-1,3-thiazol-5-ylsulfonamide.

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.41 (2H, d, J=7.9Hz), 7.27 (2H, d, J=7.9Hz), 7.20 (1H, s), 4.45 (2H, t, J=6.9Hz), 3.08 (2H, t, J=6.6Hz), 2.79 (2H, q, J=7.7Hz), 2.71 (3H, s), 2.68(3H, s), 1.36 (3H, t, J=7.7Hz)

m.p. 168.3-169.0 °C

MS (ESI) m/z: 587 [(M+H)⁺], 585 [(M-H)⁻]

EXAMPLE 282

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-

5 YL]PHENYL}ETHYL(5-CHLORO-1,3-DIMETHYL-1H-PYRAZOL-4-

YL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in step 2 of Example 243 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl} ethyl phenyl carbonate and 5-chloro-1,3-dimethyl-1H-pyrazol-4-yl sulfonamide.

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.41 (2H, d, J=7.9Hz), 7.27 (2H, d, J=7.9Hz), 7.20 (1H, s), 4.45 (2H, t, J=6.9Hz), 3.08 (2H, t, J=6.6Hz), 2.79 (2H, q, J=7.7Hz), 2.71 (3H, s), 2.68(3H, s), 1.36 (3H, t, J=7.7Hz)

m.p. 192.0-192.7 °C

MS (ESI) m/z: 604 [(M+H)⁺], 602 [(M-H)⁻]

EXAMPLE 283

2-{4-[5-CHORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-

YL]PHENYL}PROPYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-(4-aminophenyl)1-propanol

To a stirred solution of 2-(4-amino-phenyl)-propionic acid ethyl ester (5.0 g, 25.9 mmol, Takahashi, I. et al., *Heterocycles* 1996, 43, 2343-2346.) in tetrahydrofuran (200 ml) was slowly added lithiumaluminium hydride (1.96 g, 51.8 mmol), and the mixture was stirred at room temperature for 14 h. The reaction mixture was quenched with 25% ammonia solution (50ml) under ice-bath cooling. The resulting precipitate was filtered off, and the filtrate concentrated under reduced pressure to afford 3.88 g (99%) of the title compound as slight brown syrup.

¹H-NMR (CDCl₃) δ: 7.03 (2H, d, J=8.5 Hz), 6.66 (2H, d, J=8.5 Hz), 3.70-3.57 (4H, m), 2.90-2.78 (1H, m), 1.34-1.30 (1H, m), 1.22 (3H, d, J=7.1 Hz).

MS (EI) m/z: 151 (M⁺).

STEP 2. 2-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)-1-propanol

The title compound was prepared according to the procedure described in step 5 of Example 266 from 2-(4-aminophenyl)-1-propanol (step 1)

¹H-NMR (CDCl₃) δ: 9.69 (1H, br.s), 8.58 (1H, s), 7.38 (2H, d, J=8.3Hz), 7.21-7.26 (3H, m), 3.77 (2H, m), 3.03 (1H, m), 1.41 (1H, t, J=5.7Hz), 1.33 (3H, d, J=7.1 Hz)

STEP 3. 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)-1-propanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-(4-{[5-chloro-2-nitro-4-

(trifluoromethyl)phenyl]amino}phenyl)-1-propanol (step2)

¹H-NMR (CDCl₃) δ: 7.21-7.26 (3H, m), 7.07 (1H, s), 6.93 (2H, d, J=8.4 Hz), 5.41 (1H, br.s), 3.68-3.69 (2H, br.s), 2.93 (1H, m), 1.38 (1H, br.s), 1.28 (3H, d, J=7.1 Hz)

STEP 4. 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}-1-propanol

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)-1-propanol (step 3).

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.49 (2H, d, J=2.3 Hz), 7.30 (2H, d, J=8.4 Hz), 7.22 (1H, s), 3.83 (2H, m), 3.11 (1H, m), 2.80 (2H, q, J=7.6 Hz) 1.57 (1H, m), 1.33-1.40 (6H, m).

STEP 5. 2-{4-[5-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}-1,1-dimethylethyl(4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-1-propanol (step 4).

¹H-NMR (CDCl₃) δ: 8.11 (1H, s), 7.904 (2H, d, J=8.4Hz), 7.40 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.4 Hz), 7.27 (1H, s), 7.24 (1H, s), 7.20 (1H, s), 4.19-4.30 (2H, m), 3.20 (1H, m), 2.78 (2H, q, J=7.5Hz), 2.43 (3H, s), 1.53 (3H, t, J=7.56Hz), 1.34 (3H, t, J=6.9Hz)

m.p. 179.9-180.5 °C

MS (ESI) m/z: 581 [(M+H)⁺], 579 [(M-H)⁻]

EXAMPLE 284

2-[4-(5-ACETYL-2-ETHYL-1*H*-BENZIMIDAZOL-1-YL)PHENYL]-1,1-DIMETHYLETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 1-(4-{[4-hydroxy-2-methylpropyl]phenyl}amino)-3-nitrophenyl)ethanone

The title compound was prepared according to the procedure described in step 5 of Example 266 from 1-(4-aminophenyl)-2-methyl-2-propanol

¹H-NMR (CDCl₃) δ: 9.85 (1H, br.s), 8.83 (1H, s), 7.97 (1H, d, J=9.0Hz), 7.10-7.40 (4H, m), 2.82 (2H, s), 2.58 (3H, s), 1.28 (6H, s)

STEP 2. 1-(3-amino-4-{[4-(2-hydroxy-2-methylpropyl)phenyl]amino}phenyl)ethanone

The title compound was prepared according to the procedure described in step 2 of Example 28 from 1-(4-{[4-hydroxy-2-methylpropyl]phenyl}amino)-3-nitrophenyl)ethanone (step1)

¹H-NMR (CDCl₃) δ: 7.38-7.46 (2H, m), 7.16 (2H, dd, J= 8.4 Hz), 6.96 (2H, d, J= 8.4 Hz), 5.62 (2H, br.s), 3.60 (1H, br.s), 2.73 (2H, s), 2.54 (3H, s), 1.39 (1H, br.s), 1.24 (6H, s)

STEP 3. 1-{2-ethyl-1-[4-(2-hydroxy-2-methylpropyl)phenyl]-1H-benzimidazol-5-yl}ethanone

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-(3-amino-4-{[4-(2-hydroxy-2-methylpropyl)phenyl]amino}phenyl)ethanone (step 2).

¹H-NMR (CDCl₃) δ: 8.40 (1H, s), 7.90 (1H, d, J= 8.6 Hz), 7.46 (2H, d, J= 8.1 Hz), 7.30 (2H, d, J= 8.1 Hz), 7.14 (1H, d, J=8.6 Hz), 2.96 (2H, s), 2.82 (2H, q, J= 7.6 Hz), 2.68 (3H, s), 1.63 (1H, br.s), 1.38 (3H, t, J= 7.6 Hz), 1.32 (6H, s)

STEP 4. 2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]-1,1-dimethylethyl(4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 1-{2-ethyl-1-[4-(2-hydroxy-2-methylpropyl)phenyl]-1H-benzimidazol-5-yl}ethanone (step 3).

¹H-NMR (CDCl₃) δ: 8.41 (1H, s), 7.88-7.95 (3H, m), 7.09-7.35 (7H, m), 3.14 (2H, s), 2.80 (2H, q, J=7.6Hz), 2.68 (3H, s), 2.40 (3H, s), 1.45 (6H, s), 1.38 (3H, t, J=7.6Hz)

m.p. 103.4-104.2 °C

MS (ESI) m/z: 534 [(M+H)⁺], 532 [(M-H)⁻]

EXAMPLE 285

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(5-METHYL-2-PYRIDINYL)SULFONYLCARBAMATE MONO-HYDROCHLORIDE

The title compound was prepared according to the procedure described in step 2 of Example 243 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl phenyl carbonate.

¹H-NMR (CDCl₃) δ: 8.57 (1H, s), 8.15 (1H, s), 8.12 (1H, d, J=8.0Hz), 7.77 (1H, d, J=7.9Hz), 7.37 (1H, d, J=7.9Hz), 7.17-7.25 (4H, m), 4.36 (2H, t, J=6.6Hz), 3.00 (2H, t, J=6.6Hz), 2.77 (2H, q, J=7.5Hz), 2.46 (3H, s), 1.36 (3H, t, J=7.3Hz)
m.p. 205.8 °C

MS (ESI) m/z: 567 [(M+H)⁺], 565 [(M-H)⁻]

EXAMPLE 286

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(5-METHYL-2-PYRIDINYL)SULFONYLCARBAMATE MONO-HYDROCHLORIDE MONO-HYDROCHLORIDE

The title compound was prepared according to the procedure described Example 240 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl} ethyl(5-methyl-2-pyridinyl)sulfonylcarbamate (Example 285).

¹H-NMR (CDCl₃) δ: 8.53 (1H, s), 8.49 (1H, s), 8.08 (1H, d, J=7.6Hz), 7.78 (1H, d, J=6.8 Hz), 7.53 (2H, br.s), 7.41 (3H, br.s), 4.38 (2H, t, J=5.9Hz), 3.21 (2H, br.s), 3.07 (2H, t, J=5.9 Hz), 2.47 (3H, s), 1.51 (3H, br.s)
m.p. 200.2 °C

MS (ESI) m/z: 567 [(M+H)⁺], 565 [(M-H)⁻]

EXAMPLE 287

2-{5-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-YL]-3-PYRIDINYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. benzyl ethyl 2-(6-nitro-3-pyridinyl)malonate

To a mixture of 5-bromo-2-nitropyridine (8.66 g, 42.7 mmol) and benzyl ethyl malonate (9.50 g, 42.7 mmol) in tetrahydrofuran (160 ml) and

dimethylformamide (40 ml) was added K_2CO_3 (5.90 g, 42.7 mmol) and stirred under reflux temperature for 20 h. The mixture was diluted with water (1 l) and extracted with ethyl acetate (3 x 200 ml). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give 5.26 g of title compound as

5 orange oil.

1H -NMR ($CDCl_3$) δ : 8.61 (1H, d, $J=2.2$ Hz), 8.26 (1H, d, $J=8.4$ Hz), 8.19 (1H, dd, $J=2.1, 8.6$ Hz), 7.29-7.38 (5H, m), 5.22 (2H, d, $J=3.6$ Hz), 4.84 (1H, s), 4.22 (2H, m), 1.23 (3H, t, $J=7.1$ Hz).

STEP 2. ethyl (6-nitro-3-pyridinyl)acetate

10 To a solution of benzyl ethyl 2-(6-nitro-3-pyridinyl)malonate (5.26 g, 15.3 mmol,) in ethanol was added palladium on carbon (530 mg) and stirred for 6 h under hydrogen atmosphere at room temperature. The catalyst was filtered off through a pad of celite and the filtrate was concentrated to give a title compound as yellow brown oil.

15 1H -NMR ($CDCl_3$) δ : 7.95 (1H, d, $J=1.8$ Hz), 7.40 (1H, dd, $J=2.4, 8.4$ Hz), 6.48 (1H, d, $J=8.4$ Hz), 4.42 (2H, br.s), 4.14 (2H, q, $J=7.1$ Hz), 3.46 (2H, s), 1.26 (3H, t, $J=7.1$ Hz).

STEP 3. 2-(6-amino-3-pyridinyl)ethanol

20 To a solution of ethyl (6-nitro-3-pyridinyl)acetate (468 mg, 2.60 mmol) in tetrahydrofuran was added $LiAlH_4$ and stirred for 2 h at room temperature. The reaction was quenched with saturated 25 % NH_3 aqueous solution and the precipitate was removed. The filtrate was concentrated to give a title compound as yellow oil.

25 1H -NMR ($CDCl_3$) δ : 7.73 (1H, d, $J=2.8$ Hz), 7.23 (1H, dd, $J=8.6$ Hz), 6.37 (1H, d, $J=2.6, 8.1$ Hz), 5.63 (2H, br.s), 3.49 (2H, t, $J=7.3$ Hz), 2.51 (2H, t, $J=7.3$ Hz). MS (EI) m/z : 138 (M^+).

STEP 4. (6-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}-3-pyridinyl)ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2-(6-amino-3-pyridinyl)ethanol (step 3).

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 8.49 (1H, s), 8.32 (1H, d, $J=2.2$ Hz), 7.64 (1H, dd, $J=2.4$, 8.4 Hz), 7.36 (1Hs), 6.97 (1H, d, $J=8.4$ Hz), 3.91 (2H, t, $J=6.5$ Hz), 2.89 (2H, t, $J=6.5$ Hz)

MS (EI) m/z : 361 (M^+).

10 STEP 5. (6-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}-3-pyridinyl)ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from (6-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}-3-pyridinyl)ethanol (step 4).

MS (EI) m/z : 331 (M^+).

15 STEP 6. 2-{6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-3-pyridinyl}ethylpropionate

- To (6-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}-3-pyridinyl)ethanol (787 mg, 2.37 mmol, from step 5) was added propionic acid and propionic anhydride and stirred at 120 °C for 15 h. The mixture was
20 quenched with NaOH and extracted with dichloromethane (3 x 30 ml). The organic layer was washed with brine, dried (MgSO_4) and concentrated to give 5.26 g of title compound as orange oil.

- 25 $^1\text{H-NMR}$ (CDCl_3) δ : 8.58 (1H, d, $J=1.9$ Hz), 8.12 (1H, s), 7.83 (1H, dd, $J=2.2$, 8.1 Hz), 7.45 (1H, s), 7.39 (1H, d, $J=8.1$ Hz), 4.40 (2H, t, $J=6.8$ Hz), 4.12 (2H, q, $J=7.3$ Hz), 3.10 (2H, t, $J=6.5$ Hz), 2.99 (2H, q, $J=7.6$ Hz), 2.29-2.44 (2H, m), 1.38 (3H, t, $J=7.4$ Hz), 1.15 (3H, t, $J=7.6$ Hz).

STEP 5. 2-{6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-3-pyridinyl}ethanol

The title compound was prepared according to the procedure described in step 8 of Example 266 from 2-{6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-pyridinyl}ethylpropionate (step 4).

¹H-NMR (CDCl₃) δ: 8.60 (1H, d, J=2.3 Hz), 8.11 (1H, s), 7.91 (1H, dd, J=2.5, 8.0 Hz), 7.45 (1H, s), 7.38 (1H, d, J=8.1 Hz), 4.01 (1H, t, J=6.2 Hz), 3.72-3.77 (2H, m), 2.94-3.04 (2H, m), 1.38 (3H, t, J=7.4 Hz).

STEP 6. 2-{6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-3-pyridinyl}ethyl-(4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-pyridinyl}ethanol (step5).

¹H-NMR (CDCl₃) δ: 8.33 (1H, d, J=1.9 Hz), 8.08 (1H, s), 7.91 (2H, d, J=8.4 Hz), 7.70 (1H, dd, J=2.4, 8.1 Hz), 7.29-7.42 (4H, m), 7.20(1H, s), 4.39 (2H, t, J=6.2 Hz), 3.00 (2H, t, J=6.2 Hz), 2.93 (2H, t, J=7.6 Hz), 2.43 (3H, s), 1.32 (3H, t, J=7.4 Hz).

MS (ESI) m/z: 567 [(M+H)⁺], 565 [(M-H)⁻].

EXAMPLE 288

2-{5-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]-3-PYRIDINYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE MONO-HYDROCHLORIDE
STEP 1.

The title compound was prepared according to the procedure described in Example 240 from 2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-3-pyridinyl}ethyl-(4-methylphenyl)sulfonylcarbamate (Example 287).

0997761.101501

¹H-NMR (CDCl₃) δ: 8.40 (1H, br.s), 8.49 (1H, br.s), 8.12 (1H, br.s), 7.82 (2H, br.s), 7.65 (1H, br.s), 7.25-7.28 (2H, m), 4.40 (2H, br.s), 3.35 (1H, s), 3.12 (2H, br.s), 2.41 (3H, s), 2.43 (3H, s), 1.53 (3H, br.s).

MS (ESI) m/z: 567 [(M+H)⁺], 565 [(M-H)⁻].

5 EXAMPLE 289

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL-5-ISOQUINOLINYLSULFONYLCARBAMATE

The title compound was prepared according to the procedure described in step 2 of Example 243 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl phenyl carbonate and 5-isoquinolinyisulfonamide.

¹H-NMR (CDCl₃) δ: 9.39 (1H, s), 8.70 (2H, t, J=6.3Hz), 8.43 (1H, d, J=6.2Hz), 8.29 (1H, d, J=8.1Hz), 8.12 (1H, s), 7.78 (1H, t, J=7.6Hz), 7.16-7.33 (5H, m), 4.32 (2H, t, J=6.9Hz), 2.97 (2H, t, J=6.8Hz), 2.77 (2H, q, J=7.4Hz), 1.346 (3H, t,

J=7.4Hz)

MS (ESI) m/z: 603 [(M+H)⁺], 601 [(M-H)⁻]

EXAMPLE 290

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL-5-QUINOLINYLSULFONYLCARBAMATE

The title compound was prepared according to the procedure described in step 2 of Example 243 from 4-(6-chloro-2-ethyl-5-trifluoromethyl-1-benzimidazol-1-yl)phenethyl-(4-methylphenyl)sulfonyl carbamate and 5-quinolinyisulfonamide

¹H-NMR (CDCl₃) δ: 8.43 (1H, d, J=8.6Hz), 8.20-8.25 (2H, m), 8.13 (1H, s), 8.12 (1H, s), 7.81-7.91 (2H, m), 7.68-7.72 (1H, m), 7.30-7.34 (2H, m), 7.12-

7.16 (3H, m), 4.37 (2H, t, J=6.6Hz), 2.98 (2H, t, J=6.3Hz), 2.74 (2H, q, J=7.4Hz), 1.35 (3H, t, J=7.4Hz).

MS (ESI) m/z: 567 [(M+H)⁺], 565 [(M-H)⁻]

EXAMPLE 291

- 5 2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL-[5-(DIMETHYLAMINO)-1-
NAPHTHNYL]SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in step 2 of Example 243 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl} ethyl phenyl carbonate and 5-(dimethylamino)-1-naphthnysulfonamide.

¹H-NMR (CDCl₃) δ: 8.61 (1H, d, J=8.4Hz), 8.46 (1H, dd, J=1.2, 7.5Hz), 8.12 (1H, s), 87.58 (2H, t, J=8.3Hz), 7.12-7.24 (6H, m), 4.30 (2H, t, J=6.8Hz), 2.93 (2H, t, J=6.8Hz), 2.75 (2H, q, J=7.5Hz), 1.35 (3H, t, J=7.5Hz)

- 15 m.p. 203.4 °C

MS (ESI) m/z: 645 [(M+H)⁺], 643 [(M-H)⁻]

EXAMPLE 292

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL-(1-METHYL-1H-IMIDAZOL-4-YL)SULFONYLCARBAMATE

- 20 The title compound was prepared according to the procedure described in step 2 of Example 243 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl} ethyl phenyl carbonate and 1-methyl-1H-imidazol-4-ylsulfonamide.

¹H-NMR (CDCl₃) δ: 8.13 (1H, s), 7.72 (1H, d, J=1.5Hz), 7.55 (1H, d, J=1.3Hz), 7.41 (2H, d, J=8.2Hz), 7.26 (2H, d, J=8.2Hz), 7.20 (1H, s), 4.38 (2H, t, J=6.6Hz), 3.78 (3H, s), 3.04 (2H, d, J=6.8Hz), 2.79 (2H, q, J=7.6Hz), 1.36 (3H, t, J=7.6Hz)

m.p. 204.3 °C

MS (ESI) m/z: 556 [(M+H)⁺], 554 [(M-H)⁻]

EXAMPLE 293

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL-(1-METHYL-1H-IMIDAZOL-4-YL)SULFONYLCARBAMATE

5 MONO HYDROCHLORIDE

The title compound was prepared according to the procedure described in Example 240 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl-(1-methyl-1H-imidazol-4-yl)sulfonylcarbamate (Example 292).

10 MS (ESI) m/z: 556 [(M+H)⁺], 554 [(M-H)⁻]

EXAMPLE 294

2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL-(1,2-DIMETHYL-1H-IMIDAZOL-4-YL)SULFONYLCARBAMATE

15 The title compound was prepared according to the procedure described in step 2 of Example 243 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl phenyl carbonate and 1,2-dimethyl-1H-imidazol-4-ylsulfonamide.

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.63 (1H, s), 7.41 (2H, d, J=8.2Hz), 7.25 (2H, d, J=8.2Hz), 7.19 (1H, s), 4.37 (2H, t, J=6.8Hz), 3.64 (3H, s), 3.04 (2H, d, J=6.6Hz), 2.79 (2H, q, J=7.6Hz), 2.42 (3H, s), 1.36 (3H, t, J=7.6Hz)
20 m.p. 221.2 °C

MS (ESI) m/z: 570 [(M+H)⁺], 568 [(M-H)⁻]

EXAMPLE 295

25 2-{4-[6-CHLORO-2-ETHYL-5-(TRIFLUOROMETHYL)-1H-
BENZIMIDAZOL-1-YL]PHENYL}ETHYL-(1,2-DIMETHYL-1H-
IMIDAZOL-4-YL)SULFONYLCARBAMATE DI-HYDROCHLORIDE

The title compound was prepared according to the procedure described in Example 240 from 2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-

benzimidazol-1-yl]phenyl}ethyl-(1,2-dimethyl-1*H*-imidazol-4-yl)sulfonylcarbamate (Example 294).

MS (ESI) *m/z*: 570 [(*M*+*H*)⁺], 568 [(*M*-*H*)⁻]

EXAMPLE 296

- 5 2-{4-[5,7-DIMETHYL-2-(1*H*-PYRAZOL-3-YL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE-3-YL]-PHENYL}ETHYL(4-METHYLPHENYL)SUFONYLCARBAMATE

STEP 1. 2-{4-[5,7-dimethyl-2-(1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]phenyl}ethanol

- 10 The title compound was prepared according to the procedure described in step 1 of Example 236 from 4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenylethanol.

¹H-NMR (DMSO-*d*₆) δ: 13.15 (1H, br.s), 7.77 (3H, s), 7.35 (2H, d, *J*=7.7 Hz), 7.25 (2H, d, *J*=7.7 Hz), 7.02 (1H, s), 6.53 (1H, s), 4.75 (2H, t, *J*=4.8 Hz), 3.71 (2H, q, *J*=6.8 Hz), 2.81 (1H, t, *J*=6.6 Hz), 2.58 (3H, s), 2.42 (3H, s)

- 15 STEP 2. 2-{4-[5,7-dimethyl-2-(1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-3-yl]-phenyl}ethyl(4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[5,7-dimethyl-2-(1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]phenyl}ethanol (step 1).

¹H-NMR (DMSO-*d*₆) δ: 13.14 (1H, br.s), 7.69-7.78 (3H, m), 7.21-7.43 (6H, m), 7.02 (1H, s), 6.52 (1H, s), 4.18 (2H, t, *J*=6.4 Hz), 2.89 (2H, t, *J*=6.4 Hz), 2.58 (2H, s), 2.41(3H, s), 2.32 (3H, s)

MS (ESI) *m/z*: 531 (*M*⁺), 529 [(*M*-*H*)⁻]

- 25 EXAMPLE 297

2-{4-[5,7-DIMETHYL-2-(1H-PYRAZOL-3-YL)-3H-IMIDAZO[4,5-b]PYRIDINE-3-YL]PHENYL}ETHYL(4-METHYLPHENYL)SUFONYLCARBAMATE SODIUM SALT
STEP 1. 2-{4-[5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in Example 2 from 2-{4-[5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridine-3-yl]-phenyl}ethyl(4-methylphenyl)sulfonylcarbamate (Example 296).

¹H-NMR (CDCl₃) δ: 9.85 (1H, s), 8.37 (1H, d, J=8.4 Hz), 7.31 (1H, d, J=2.0 Hz), 7.14 (1H, dd, J=2.0, 8.3 Hz), 6.60 (1H, s), 3.87 (2H, dt, J=6.2, 6.4 Hz), 2.84 (2H, t, J= 6.4Hz), 2.56 (3H, s), 2.46 (3H, s), 1.40 (1H, t, J= 6.2Hz).

MS (ESI) m/z: 531 (MH⁺), 529 ([M-H]⁻)

EXAMPLE 298

N-{(2-{4-[5,7-DIMETHYL-2-(1H-PYRAZOL-3-YL)-3H-IMIDAZO[4,5-B]PYRIDINE-3-YL]PHENYL}ETHYL)AMINO}CARBONYL}-4-METHYLBENZENESULFONAMIDE

STEP 1. 3-[4-(2-chloroethyl)phenyl]-5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl}ethanol (Example 297, step 1).

¹H-NMR (CDCl₃) δ: 13.15 (1H, s), 7.77 (2H, br.s), 7.43 (2H, br.s), 7.20 (2H, br.s), 7.04 (1H, s), 6.54 (1H, br.s), 3.96 (2H, t, J= 6.8 Hz), 3.15 (2H, tm J=6.8 Hz), 2.60 (3H, s), 2.30 (3H, s).

STEP 2. 3-[4-(2-azidoethyl)phenyl]-5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in step 5 of Example 1 from 3-[4-(2-chloroethyl)phenyl]-5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridine (step 1).

¹H-NMR (DMSO-d₆) δ: 13.15 (1H, br.s), 9.85 (1H, br.s), 7.76 (1H, br.s), 7.41 (2H, d, J= 8.1 Hz), 7.31 (2H, d, J= 8.1 Hz), 7.04 (1H, s), 6.53 (1H, s), 3.69 (2H, t, J= 6.6 Hz), 2.95 (2H, t, J= 6.8 Hz), 2.58 (3H, s), 2.42 (3H, s), MS (EI) m/z: 358 (M⁺).

STEP 3. 2-{4-[5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl}ethanamine

The title compound was prepared according to the procedure described in step 6 of Example 1 from 3-[4-(2-azidoethyl)phenyl]-5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridine (step 2).

¹H-NMR (DMSO-d₆) δ: 9.83 (1H, br.s), 7.68 (2H, br.s), 7.23-7.43 (5H, m), 7.04 (1H, s), 5.75 (1H, s), 2.68-2.90 (4H, m), 2.59 (3H, s), 2.42 (3H, s),

MS (EI) m/z: 332 (M⁺).

STEP 4. N-[(2-{4-[5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridine-3-yl]phenyl}ethyl)amino]carbonyl]-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-{4-[5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl}ethanamine (step3)

¹H-NMR (CD₃OD) δ: 7.80 (2H, d, J= 8.2 Hz), 7.58 (1H, br.s), 7.20-7.35 (6H, m), 7.08 (1H, s), 6.20 (1H, br.s), 3.42 (2H, t, J=6.8 Hz), 2.84 (2H, t, J=6.9 Hz), 2.68 (2H, s), 2.50 (3H, s), 2.34 (3H, s)

MS (ESI) m/z: 530 (MH⁺), 528 ([M-H]⁻)

EXAMPLE 299

2-[4-(5-CYANO-2-ETHYL-6-METHYL-1H-BENZIMIDAZOL-1-YL)PHENYL]ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 4-Chloro-2-methyl-5-nitrobenzonitrile

To a solution of 4-chloro-2-methyl-5-nitrobenzonitrile (10g, 66 mmol) in conc. H₂SO₄ was added KNO₃ (7.0 g, 69.3 mmol) at 0 °C in small portions, and then the reaction mixture was stirred overnight at ambient temperature. It was then poured into ice and extracted with AcOEt. The combined extracts were washed by sat. NaHCO₃ aq., dried over MgSO₄ and concentrated. The resulting precipitates were collected by filtration, washed with ether, and dried under reduced pressure to give 5.5 g (42%) of the title compound.

¹H-NMR (CDCl₃) δ: 8.19 (1H, s), 7.57 (1H, s), 2.64 (3H, s).

STEP 2. 4-{{[4-(2-hydroxyethyl)phenyl]amino}-2-methyl-5-nitrobenzonitrile

The title compound was prepared according to the procedure described in step 3 of Example 1 from 3-bromo-6-chloro-2,4-dimethyl-5-nitropyridine (step 2).

¹H-NMR (CDCl₃) δ: 9.76 (1H, br.s), 8.51 (1H, s), 7.36 (1H, d, J=8.4Hz), 7.22 (1H, d, J=8.3Hz), 6.96 (1H, s), 3.94 (2H, dd, J=11.7, 6.2Hz), 2.94 (2H, t, J=6.4Hz), 2.42 (3H, s)

STEP 3. 5-amino-4-{{[4-(2-hydroxyethyl)phenyl]amino}-2-methylbenzonitrile

The title compound was prepared according to the procedure described in step 4 of Example 1 from 2-{{4-[(5-bromo-4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl}ethanol (step 3).

¹H-NMR (CDCl₃) δ: 7.19 (1H, d, J=8.4Hz), 6.94-7.00 (4H, m), 5.59 (1H, br.s), 3.84-3.90 (2H, m), 3.50 (2H, br.s), 2.85 (2H, t, J=6.4Hz), 2.37 (3H, s).

STEP 5. 2-[4-(5-cyano-2-ethyl-6-methyl-1H-benzimidazo-1-yl)phenyl]ethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{{4-[(3-amino-5-bromo-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethanol (step 4).

MS (EI) m/z: 361 (M⁺)

STEP 6. 2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-6-methyl-1*H*-benzimidazole-5-carbonitrile

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-bromo-2-isopropyl-5,7-dimethyl-3*H*-

5 imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl 2-methylpropanoate (step 5).

¹H-NMR (CDCl₃) δ: 8.00 (1H, s), 7.50 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 6.98(1H, s), 4.01 (2H, t, J=6.4 Hz), 3.03 (2H, t, J=6.6Hz), 2.79 (2H, q, J=7.5Hz), 2.56 (3H, s), 1.35 (3H, t, J=7.5Hz)

STEP 7. 2-[4-(5-cyano-2-ethyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl(4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-6-methyl-1*H*-benzimidazole-5-carbonitrile (step 6).

¹H-NMR (CDCl₃) δ: 8.03 (1H, s), 7.92 (2H, d, J=8.4 Hz), 7.39 (2H, d, J=8.4 Hz), 7.35 (2H, d, J=8.1 Hz), 7.26 (2H, d, J=8.1 Hz), 6.96(1H, s), 4.39 (2H, t, J=6.8 Hz), 3.04 (2H, t, J=6.6Hz), 2.77 (2H, q, J=7.7 Hz), 2.57 (3H, s), 2.44 (3H, s), 1.35 (3H, t, J=7.5Hz)

EXAMPLE 300

N-[(2-[4-(5-CYANO-2-ETHYL-6-METHYL-1*H*-BENZIMIDAZOL-1-

YL)PHENYL]ETHYL}AMINO)CARBONYL](4-

METHYLBENZENESULFOAMIDE

STEP 1. 1-[4-(2-chloroethyl)phenyl]-2-ethyl-6-methyl-1*H*-benzimidazole-5-carbonitrile

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(6-bromo-2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethanol (step 6).

¹H-NMR (CDCl₃) δ: 8.02 (1H, s), 7.48 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 6.96-6.98 (1H, m), 3.83 (2H, t, J=7.1 Hz), 3.21 (2H, t, J=7.0 Hz), 2.78 (2H, q, J=7.5Hz), 2.58 (3H, s), 1.35 (3H, t, J=7.5 Hz).

STEP 2. 1-[4-(2-azidoethyl)phenyl]-2-ethyl-6-methyl-1*H*-benzimidazole-5-carbonitrile

The title compound was prepared according to the procedure described in step 8 of Example 1 from 6-bromo-3-[4-(2-chloroethyl)phenyl]-2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (step 7).

MS (EI) m/z: 412 (M⁺)

¹H-NMR (CDCl₃) δ: 8.02 (1H, s), 7.48 (2H, d, J=8.0 Hz), 7.30 (2H, d, J=8.2 Hz), 6.95 (1H, s), 3.63 (2H, t, J=6.8 Hz), 3.03 (2H, t, J=7.0 Hz), 2.78 (2H, q, J=7.5Hz), 2.57 (3H, s), 1.35 (3H, t, J=7.3 Hz).

STEP 3. 1-[4-(2-aminoethyl)phenyl]-2-ethyl-6-methyl-1*H*-benzimidazole-5-carbonitrile

The title compound was prepared according to the procedure described in step 9 of Example 1 from 2-[4-(6-bromo-2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl azide (step 8).

¹H-NMR (CDCl₃) δ: 7.49 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 6.93 (1H, s), 6.60 (2H, br.s), 3.32-3.00 (5H, m), 2.65 (3H, s), 2.48 (3H, s), 1.31 (6H, d, J=6.8 Hz).

STEP 4. *N*-[(2-[4-(5-cyano-2-ethyl-6-methyl-1*H*-benzimidazol-1-yl)phenyl]ethyl}amino)carbonyl](4-methylbenzenesulfoamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from [4-(2-isopropyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethylamine (step 9).

¹H-NMR (CDCl₃) δ: 8.00 (1H, s), 7.72 (2H, d, J=8.4 Hz), 7.42 (2H, d, J=8.4 Hz), 7.28-7.32 (4H, m), 6.95(1H, m), 3.56-3.63 (2H, m), 2.96 (2H, t, J=7.1 Hz), 2.78 (2H, q, J=7.7 Hz), 2.54 (3H, s), 2.41 (3H, s), 1.34 (3H, t, J=7.5Hz)

EXAMPLE 301

5 2-AMINO-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE DI-HYDROCHLORIDE

STEP 1. 2-AMINO-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE

To a stirred solution of *N*-{[(2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl)ethyl]amino}carbonyl]-4-methylbenzenesulfonamide (300 mg, 0.66 mmol) in THF (6 ml) was added a solution of BrCN (175 mg, 1.65 mmol) in water (2 ml). The resultant mixture was stirred at room temperature for 16 hours. The mixture was diluted with CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄ and filtered. After concentration in vacuo, the residue was purified by preparative TLC (CH₂Cl₂/MeOH = 10/1) to afford 224 mg (71%) of the title compound.

¹H-NMR (DMSO-*d*₆) δ: 10.82 (1H, s), 8.54 (2H, s), 7.79 (2H, d, J=8.3 Hz),

7.51-7.40 (6H, m), 7.06 (1H, s), 6.91 (1H, t, J=5.5 Hz), 3.29-3.24 (2H, m), 2.80-2.76 (2H, m), 2.48 (3H, s), 2.38 (3H, s), 2.36 (3H, s)

MS (ESI) *m/z*: 479 ([M+H]⁺), 477 ([M-H]⁻)

STEP 2. 2-AMINO-5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3H-IMIDAZO[4,5-*b*]PYRIDINE DI-HYDROCHLORIDE

The title compound was prepared according to the procedure described in Example 240 from 2-amino-5,7-dimethyl-3-(4-{2-[(4-

methylphenyl)sulfonyl]amino} carbonyl]amino}ethyl} phenyl)-3*H*-imidazo[4,5-*b*]pyridine.

MS (ESI) *m/z*: 479 ([*M*+*H*]⁺), 477 ([*M*-*H*]⁻)

EXAMPLE 302

5 5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO} CARBONYL)AMINO}ETHYL}PHENYL)-2-(METHYLSULFANYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE

A mixture of *N*-{[(2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide
10 (110 mg, 0.24 mmol), di-2-pyridylthiocarbonate (68 mg, 0.29 mmol), and THF (5 ml) was stirred at room temperature for 3 days. The mixture was diluted with CH₂Cl₂ and washed with 0.1M HCl and brine. The organic fraction was dried over MgSO₄, and filtered. The solvent was removed to give *N*-[(2-{4-[(5,7-dimethyl-2-sulfanyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]ethyl}amino)carbonyl]-4-methylbenzenesulfonamide [MS (ESI) *m/z*:
15 496 ([*M*+*H*]⁺), 494 ([*M*-*H*]⁻)]. This was dissolved with THF (2 ml), then 1M NaOMe in MeOH (0.49 ml) and MeI (45 μl, 0.73 mmol) was added to the mixture at room temperature. After 1 hour, the mixture was evaporated in vacuo and the residue was purified by preparative TLC (CH₂Cl₂/MeOH = 10/1) to
20 afford 31 mg (25%) of the title compounds.

¹H-NMR (CDCl₃) δ: 7.86 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.1Hz), 7.22-7.16 (4H, m), 6.88 (1H, s), 6.02 (1H, t, J=5.6 Hz), 3.51-3.45 (2H, m), 2.83 (2h, t, J=6.2Hz), 2.67 (3H, s), 2.62 (3H, s), 2.42 (3H, s), 2.417 (3H, s)

MS (ESI) *m/z*: 510 ([*M*+*H*]⁺), 508 ([*M*-*H*]⁻)

25 EXAMPLE 303

0997751.101501
T05107.15772660

5,7-DIMETHYL-2-(METHYLAMINO)-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE

A mixture of *N*-{[(2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (300 mg, 0.66 mmol), methylisothiocyanate (56 μ l, 0.86 mmol), and THF (6 ml) was stirred at room temperature for 3 days. The solvent was removed to give *N*-{[(2-{4-[(4,6-dimethyl-[(methylamino)carbonothioyl]amino}-2-pyridinyl)amino]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide [MS (ESI) *m/z*: 527 ([*M*+*H*]⁺), 525 ([*M*-*H*]⁻)]. This was dissolved with MeCN (4 ml) and treated with MeI (54 μ l) at 0 °C for 20 hours. After concentration under reduced pressure, the residue was purified by preparative TLC (EtOAc/EtOH = 20/1) to afford 170 mg (52%) of the title compounds.

¹H-NMR (CD₃OD) δ : 7.72 (2H, d, *J*=8.3 Hz), 7.24 (4H, d, *J*=7.9 Hz), 7.15 (2H, d, *J*=8.4 Hz), 6.70 (1H, s), 3.28 (2H, t, *J*=7.0 Hz), 2.90 (3H, s), 2.72 (2H, t, *J*=7.0 Hz), 2.41 (3H, s), 2.26 (3H, s), 2.24 (3H, s)
MS (ESI) *m/z*: 493 ([*M*+*H*]⁺), 491 ([*M*-*H*]⁻)

EXAMPLE 304

5,7-DIMETHYL-2-(METHYLAMINO)-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE MONO-HYDROCHLORIDE

The title compound was prepared according to the procedure described in Example 240 from 5,7-dimethyl-2-(methylamino)-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine hydrochloride.

MS (ESI) *m/z*: 493 ([*M*+*H*]⁺), 491 ([*M*-*H*]⁻)

EXAMPLE 305

0997751-101501

N-[5,7-DIMETHYL-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDIN-2-YL]ACETAMIDE
2-amino-5,7-dimethyl-3-(4-{2-[(4-

5 methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine (73 mg) was treated with pyridine (1 ml) and Ac₂O (0.2 ml) at room temperature for 3 hours. After evaporation in vacuo, the residue was purified by preparative TLC (hexane/acetone = 1/1) to afford 4 mg (5%) of the title compounds.

10 ¹H-NMR (CDCl₃) δ: 7.79 (2H, d, J=8.4 Hz), 7.34-7.22 (7H, m), 7.04 (1H, s), 6.30 (1H, br.s), 3.51-3.48 (2H, m), 2.87-2.83 (2H, m), 2.66 (3H, s), 2.53 (3H, s), 2.42 (3H, s), 2.26 (3H, s),
MS (ESI) *m/z*: 521 ([M+H]⁺), 519 ([M-H]⁻)

EXAMPLE 306

15 *5,7*-DIMETHYL-2-(DIMETHYLAMINO)-3-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-3*H*-IMIDAZO[4,5-*b*]PYRIDINE

To a stirred solution of 2-amino-5,7-dimethyl-3-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-3*H*-imidazo[4,5-*b*]pyridine (70 mg) in THF (1 ml) was added NaH (21 mg, 0.88 mmol) at room temperature. After 10 min, MeI (27 μl) was added to the mixture and stirred at room temperature for 2 days. The mixture was poured into ice-water and extracted with CH₂Cl₂, and the organic fraction was dried over MgSO₄, then filtered. After removal of solvent by evaporation, the residue was purified by
25 preparative TLC (CH₂Cl₂/MeOH = 10/1) to afford 27 mg (36%) of the title compounds.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.86 (2H, d, $J=8.4$ Hz), 7.32-7.24 (4H, m), 7.16 (2H, d, $J=8.4$ Hz), 6.77 (1H, s), 6.04 (1H, t, $J=5.7$ Hz), 3.50-3.44 (2H, m), 2.78 (2H, t, $J=6.3$ Hz), 2.71 (6H, s), 2.55 (3H, s), 2.41 (3H, s), 2.34 (3H, s)

MS (ESI) m/z : 507 ($[\text{M}+\text{H}]^+$), 505 ($[\text{M}-\text{H}]^-$)

5 EXAMPLE 307

2-[4-(2-AMINO-5,7-DIMETHYL-3H-IMIDAZO[4,5- b]PYRIDIN-3-
YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 2-[4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl]ethyl (4-
methylphenyl)sulfonylcarbamate

10 The title compound was prepared according to the procedure described in Example 3 from 2-[4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl]ethanol.

$^1\text{H-NMR}$ (CDCl_3) δ : 9.55 (1H, s), 7.89 (2H, d, $J=8.3$ Hz), 7.54 (2H, d, $J=8.6$ Hz), 7.32 (2H, d, $J=8.6$ Hz), 7.11 (2H, d, $J=8.4$ Hz), 6.54 (1H, s), 4.28 (2H, t, $J=7.0$ Hz), 2.88 (2H, t, $J=7.0$ Hz), 2.55 (3H, s), 2.43 (6H, s)

15 MS (ESI) m/z : 485 ($[\text{M}+\text{H}]^+$), 483 ($[\text{M}-\text{H}]^-$)

STEP 2. 2-[4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl]ethyl (4-
methylphenyl)sulfonylcarbamate

20 The title compound was prepared according to the procedure described in step 4 of Example 1 from 2-[4-[(4,6-dimethyl-3-nitro-2-pyridinyl)amino]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.82 (2H, d, $J=8.3$ Hz), 7.25 (2H, d, $J=8.3$ Hz), 6.93 (2H, d, $J=8.4$ Hz), 6.84 (2H, d, $J=8.4$ Hz), 6.66 (1H, s), 4.22 (2H, t, $J=6.6$ Hz), 2.77 (2H, t, $J=6.6$ Hz), 2.39 (3H, s), 2.37 (3H, s), 2.22 (3H, s)

25 MS (ESI) m/z : 455 ($[\text{M}+\text{H}]^+$), 453 ($[\text{M}-\text{H}]^-$)

STEP 3. 2-[4-(2-AMINO-5,7-DIMETHYL-3H-IMIDAZO[4,5- b]PYRIDIN-3-
YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 127 from 2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate.

¹H-NMR (DMSO-d₆) δ: 7.76 (2H, d, J=8.3 Hz), 7.42-7.35 (6H, m), 6.78 (1H, s),

- 5 6.61 (1H, br.s), 4.22 (2H, t, J=6.6 Hz), 2.92 (2H, d, J=6.6 Hz), 2.373 (3H, s),
2.365 (3H, s), 2.32 (3H, s)

MS (ESI) m/z: 480 ([M+H]⁺), 478 ([M-H]⁻)

EXAMPLE 308

2-{4-[5,7-DIMETHYL-2-(METHYLAMINO)-3H-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

- 10 The title compound was prepared according to the procedure described in Example 129 from 2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate.

¹H-NMR (DMSO-d₆) δ: 7.78 (2H, d, J=8.1 Hz), 7.43-7.33 (7H, m), 6.77 (1H, s),

- 15 6.43 (1H, br.s), 4.25 (2H, t, J=6.6 Hz), 2.93 (2H, t, J=6.6 Hz), 2.88 (3H, s), 2.41
(3H, s), 2.37 (3H, s), 2.31 (3H, s)

MS (ESI) m/z: 494 ([M+H]⁺), 492 ([M-H]⁻)

EXAMPLE 309

2-{4-[5,7-DIMETHYL-2-(METHYLSULFANYL)-3H-IMIDAZO[4,5-*b*]PYRIDIN-3-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

- 20 The title compound was prepared according to the procedure described in Example 128 from 2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate.

- 25 ¹H-NMR (CDCl₃) δ: 7.92 (2H, d, J=8.4 Hz), 7.36-7.22 (6H, m), 6.88 (1H, s),
4.32 (2H, t, J=6.6 Hz), 2.93 (2H, t, J=6.6 Hz), 2.72 (3H, s), 2.62 (3H, s), 2.48
(3H, s), 2.41 (3H, s)

MS (ESI) m/z : 511 ($[M+H]^+$), 509 ($[M-H]^-$)

EXAMPLE 310

2-{4-[5,7-DIMETHYL-2-(METHYLSULFONYL)-3H-IMIDAZO[4,5-
b]PYRIDIN-3-YL]PHENYL}ETHYL (4-

5 METHYLPHENYL)SULFONYLCARBAMATE

To a stirred solution of 2-{4-[5,7-dimethyl-2-(methylsulfanyl)-3H-imidazo[4,5- b]pyridin-3-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (100 mg, 0.20 mmol) in AcOH (1 ml) was added a solution of $KMnO_4$ (62 mg, 0.39 mmol) in water (2 ml) at room temperature. After 1 hour, the mixture was
10 poured into ice-sat. $NaHCO_3$ aq. and extracted with CH_2Cl_2 . The organic layer was dried over $MgSO_4$, and the filtered. After concentration in vacuo, the residue was purified by preparative TLC ($CH_2Cl_2/MeOH = 10/1$) to afford 70 mg (66%) of the title compounds.

1H -NMR ($CDCl_3$) δ : 7.91 (2H, d, $J=8.4$ Hz), 7.47 (2H, d, $J=8.2$ Hz), 7.34-7.26
15 (4H, m), 7.08 (1H, s), 4.35 (2H, t, $J=6.7$ Hz), 3.45 (3H,s), 2.96 (2H, t, $J=6.7$ Hz), 2.68 (3H, s), 2.55 (3H, s), 2.42 (3H, s)

MS (ESI) m/z : 543 ($[M+H]^+$), 541 ($[M-H]^-$)

EXAMPLE 311

5-ACETYL-2-(METHYLAMINO)-1-(4-{2-[(4-

20 METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-1H-BENZIMIDAZOLE

The title compound was prepared according to the procedure described in Example 129 from *N*-{[(2-{4-[(4-acetyl-2-aminophenyl)amino]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide.
25

¹H-NMR (CDCl₃) δ: 8.06 (1H, s), 7.75-7.66 (3H, m), 7.38-7.26 (6H, m), 6.89 (1H, d, J=8.3 Hz), 6.60 (1H, br.s), 3.55 (2H, dd, J=12.5 and 6.6Hz), 3.08 (3H, s), 2.91 (2H, t, J=6.6 Hz), 2.61 (3H, s), 2.38 (3H, s)
MS (ESI) m/z: 506 ([M+H]⁺), 504 ([M-H]⁻)

5 EXAMPLE 312

2-{4-[6-CHLORO-2-(3-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

10 STEP 1. 2-{4-[6-CHLORO-2-(3-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHANOL

The title compound was prepared according to the procedure described in Example 138 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethanol.

¹H-NMR (CDCl₃) δ: 8.70 (1H, dd, J=2.2 and 0.7 Hz), 8.62 (1H, dd, J=4.5 and 1.7 Hz), 8.23 (1H, s), 8.01-7.97 (1H, m), 7.45 (2H, dd, J=6.5 and 2.2 Hz), 7.37-7.24 (7H, m), 3.97 (2H, t, J=6.6 Hz), 2.99 (2H, t, J=6.6 Hz)
MS (ESI) m/z: 418 ([M+H]⁺), 476 ([M+CF₃CO₂]⁻)

15 STEP 2. 2-{4-[6-CHLORO-2-(3-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

20 The title compound was prepared according to the procedure described in Example 3 from 2-{4-[6-chloro-2-(3-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol.

¹H-NMR (CDCl₃) δ: 8.73 (1H, dd, J=4.9 and 1.8 Hz), 8.40-8.36 (1H, m), 8.23 (1H, s), 7.91 (1H, dd, J=2.2 and 0.7 Hz), 7.84-7.80 (2H, m), 7.49-7.43 (2H, m), 7.31-7.17 (6H, m), 4.44 (2H, t, J=6.2 Hz), 3.02 (2H, t, J=6.2 Hz), 2.41 (3H, s)
MS (ESI) m/z: 615 ([M+H]⁺), 613 ([M-H]⁻)

EXAMPLE 313

2-{4-[6-CHLORO-2-(4-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

- 5 STEP 1. 2-{4-[6-CHLORO-2-(4-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHANOL

The title compound was prepared according to the procedure described in Example 138 from 2-{4-[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl}ethanol.

- 10 ¹H-NMR (CDCl₃) δ: 8.60 (2H, dd, J=4.6 and 1.7 Hz), 8.25 (1H, s), 7.49-7.44 (4H, m), 7.37 (1H, s), 7.27-7.23 (2H, m), 4.00 (2H, t, J=6.4 Hz), 3.02 (2H, t, J=6.4 Hz)

MS (ESI) m/z: 418 ([M+H]⁺), 476 ([M+CF₃CO₂]⁺)

- 15 STEP 2. 2-{4-[6-CHLORO-2-(4-PYRIDINYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[6-chloro-2-(4-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol.

- 20 ¹H-NMR (CDCl₃) δ: 8.60 (2H, dd, J=4.8 and 1.5 Hz), 8.27 (1H, s), 7.89 (2H, d, J=8.3 Hz), 7.44-7.18 (9H, m), 4.39 (2H, t, J=6.4 Hz), 3.03 (2H, t, J=6.4 Hz), 2.40 (3H, s)

MS (ESI) m/z: 615 ([M+H]⁺), 613 ([M-H]⁻)

EXAMPLE 314

- 25 2-{4-[6-CHLORO-2-(2-METHYLPHENYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[6-CHLORO-2-(2-METHYLPHENYL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHANOL

The title compound was prepared according to the procedure described in Example 138 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)

5 phenyl]amino}phenyl)ethanol.

¹H-NMR (CDCl₃) δ: 8.22 (1H, s), 7.47 (1H, s), 7.33-7.10 (8H, m), 3.89 (2H, t, J=6.4 Hz), 2.89 (2H, t, J=6.4 Hz), 2.20 (3H, s)

MS (ESI) m/z: 431 ([M+H]⁺)

STEP 2. 2-{4-[6-CHLORO-2-(2-METHYLPHENYL)-5-

10 (TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[6-chloro-2-(2-methylphenyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol.

15 ¹H-NMR (CDCl₃) δ: 8.24 (1H, s), 7.78 (2H, d, J=8.2 Hz), 7.46 (1H, s), 7.35-7.09 (8H, m), 7.00 (2H, d, J=8.4 Hz), 4.27 (2H, t, J=6.8 Hz), 2.88 (2H, t, J=6.8 Hz), 2.41 (3H, s), 2.11 (3H, s)

MS (ESI) m/z: 628 ([M+H]⁺), 489 ([M+CH₃CO₂]⁺)

EXAMPLE 315

20 2-{4-[6-CHLORO-2-(1,3-THIAZOL-2-YL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[6-CHLORO-2-(1,3-THIAZOL-2-YL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHANOL

25 The title compound was prepared according to the procedure described in Example 138 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethanol.

¹H-NMR (CDCl₃) δ: 8.23 (1H, s), 7.75 (1H, d, J=3.1 Hz), 7.47-7.45 (3H, m), 7.36-7.27 (3H, m), 3.99 (2H, t, J=6.4 Hz), 3.03 (2H, t, J=6.4 Hz)
MS (ESI) m/z: 424 ([M+H]⁺), 482 ([M+CH₃CO₂]⁺)

STEP 2. 2-{4-[6-CHLORO-2-(1,3-THIAZOL-2-YL)-5-

- 5 (TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[6-chloro-2-(1,3-thiazol-2-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol.

- 10 ¹H-NMR (CDCl₃) δ: 8.23 (1H, s), 7.91 (2H, d, J=8.4 Hz), 7.74 (1H, d, J=3.1 Hz), 7.46 (1H, d, J=3.1 Hz), 7.38-7.26 (7H, m), 4.40 (2H, t, J=6.8 Hz), 3.04 (2H, t, J=6.8 Hz), 2.42 (3H, s)
MS (ESI) m/z: 621 ([M+H]⁺), 619 ([M-H]⁻)

EXAMPLE 316

- 15 2-{4-[6-CHLORO-2-(*H*-IMIDAZOL-4-YL)-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[6-CHLORO-2-(*H*-IMIDAZOL-4-YL)-5-

(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHANOL

- 20 The title compound was prepared according to the procedure described in Example 138 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethanol.

- ¹H-NMR (CDCl₃/CD₃OD=4/1) δ: 8.09 (1H, s), 7.65 (1H, s), 7.50 (2H, d, J=8.7 Hz), 7.33 (2H, d, J=8.2 Hz), 7.25 (1H, s), 6.91 (1H, s), 3.93 (2H, t, J=6.4 Hz),
25 3.00 (2H, t, J=6.4 Hz)
MS (ESI) m/z: 407 ([M+H]⁺), 405 ([M-H]⁻)

STEP 2. 2-{4-[6-CHLORO-2-(*H*-IMIDAZOL-4-YL)-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[6-chloro-2-(*H*-imidazol-4-yl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethanol.

MS (ESI) *m/z*: 604 ([*M*+*H*]⁺), 602 ([*M*-*H*]⁻)

EXAMPLE 317

2-[4-(5,6-DIMETHYL-1*H*-BENZIMIDAZOL-1-YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP. 4-(2-HYDROXYETHYL)PHENYLBORONIC ACID

To a stirred solution of 4-bromophenethylalcohol (5.00 g, 24.9 mmol) in THF (80 ml) was added a solution of 1.5*M* *n*-BuLi in hexane (39.8 ml, 59.7 mmol) at -78 °C over 30 min. After 1 hour, a solution of B(O^{*i*}Pr)₃ (8.61 ml, 37.3 mmol) in THF (20 ml) was added slowly to the mixture at -78 °C. The resultant mixture was warmed to room temperature, and treated with 2*M* HCl (100 ml) for 1 hour. This was extracted with CH₂Cl₂ and dried over MgSO₄, then filtered. After evaporation in vacuo, the residue was purified by silica-gel column chromatography eluting with CH₂Cl₂/MeOH = 20/1 to afford 2.61 g (63%) of the title compound.

¹H-NMR (CD₃OD) δ: 7.64-7.48 (2H, m), 7.19-7.13 (2H, m), 3.70 (2H, t, *J*=7.2 Hz), 2.77 (2H, t, *J*=7.2 Hz)

MS (ESI) *m/z*: 165 ([*M*-*H*]⁻)

STEP 2. 4-{2-[4-(4-

METHYLPHENYL)SULFONYL]AMINO}CARBONYL)OXY]ETHYL}PHENYLBORONIC ACID

4-(2-hydroxyethyl)phenylboronic acid (1.00 g, 6.02 mmol) was treated with pTsNCO (1.01 ml, 6.63 mmol) and pyridine (90 ml) at room temperature for 2 hours. The mixture was poured into ice-2M HCl and extracted with EtOAc. The organic layer was dried over MgSO₄, and filtered. After removal of solvent, the residue was purified by silica-gel column chromatography eluting with CH₂Cl₂/MeOH = 20/1 to afford 2.20 g (quant.) of the title compound.

¹H-NMR (DMSO-d₃) δ: 11.95 (1H, br.s), 7.97 (1H, s), 7.75-7.67 (2H, m), 7.40 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=7.7 Hz), 4.18 (2H, t, J=6.6 Hz), 2.81 (2H, t, J=6.6 Hz), 2.40 (3H, s)

MS (ESI) m/z: 381 ([M+NH₄]⁺), 362 ([M-H]⁻)

STEP 3. 2-[4-(5,6-DIMETHYL-1H-BENZIMIDAZOL-1-
YL)PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

A mixture of 4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyloxyethyl}phenylboronic acid (100 mg, 0.28 mmol), 5,6-dimethylbenzimidazole (40 mg, 0.28 mmol), Cu(OAc)₂ (60 mg, 0.33 mmol), triethylamine (115 μl, 0.83 mmol), MS4A (100 mg), and CH₂Cl₂ (4 ml) was stirred at room temperature for 1 week. After filtration through a bed of celite, the filtrate was diluted with CH₂Cl₂, and washed with water. The organic fraction was dried over MgSO₄ and filtered. After concentration under reduced pressure, the residue was purified by preparative TLC (CH₂Cl₂/MeOH = 10/1) to afford 28 mg (22%) of the title compound.

¹H-NMR (CDCl₃) δ: 7.82 (2H, d, J=8.4 Hz), 7.72 (1H, s), 7.57 (1H, s), 7.33 (2H, d, J=8.1 Hz), 7.12 (2H, d, J=8.4 Hz), 7.07 (1H, s), 7.01 (2H, d, J=8.4 Hz), 4.39 (2H, t, J=6.1 Hz), 2.94 (2H, t, J=6.1 Hz), 2.42 (3H, s), 2.39 (3H, s), 2.26 (3H, s)

MS (ESI) m/z: 464 ([M+H]⁺), 462 ([M-H]⁻)

EXAMPLE 318

6-CHLORO-5-CYANO-2-ETHYL-1-[4-{2-[{(4-METHYLPHENYL)SULFONYL}AMINO}CARBONYL)AMINO]ETHYL}PHENYL]-1H-BENZIMIDAZOLE
STEP 1. 6-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-5-

5 carbonitrile

The title compound was prepared according to the procedure described in step 7 of Example 1 from 6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazole-5-carbonitrile (Example 111, step 4).

¹H-NMR (CDCl₃) δ 8.07 (1H, s), 7.50 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz),
10 7.19 (1H, s), 3.83 (2H, t, J=7.1 Hz), 3.22 (2H, t, J=7.1 Hz), 2.79 (2H, q, J=7.5 Hz), 1.37 (3H, t, J=7.5 Hz).

STEP 2. 1-[4-(2-Azidoethyl)phenyl]-6-chloro-2-ethyl-1H-benzimidazole-5-carbonitrile

The title compound was prepared according to the procedure described in step 8 of Example 1 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-5-carbonitrile (step 1).

¹H-NMR (CDCl₃) δ 8.07 (1H, s), 7.49 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz),
15 7.18 (1H, s), 3.64 (2H, t, J=7.0 Hz), 3.04 (2H, t, J=7.0 Hz), 2.79 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

20 STEP 3. 1-[4-(2-Aminoethyl)phenyl]-6-chloro-2-ethyl-1H-benzimidazole-5-carbonitrile

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1H-benzimidazole-5-carbonitrile (step 2).

25 ¹H-NMR (CDCl₃) δ 8.06 (1H, s), 7.46 (2H, d, J=8.1 Hz), 7.26 (2H, d, J=8.1 Hz), 7.19 (1H, s), 3.09 (2H, t, J=7.1 Hz), 2.89 (2H, t, J=7.1 Hz), 2.79 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

09977761.101501

STEP 4. 6-Chloro-5-cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazole-5-carbonitrile (step 3).

mp 219-224 °C; IR (KBr) v: 3388, 2229, 1708, 1618, 1514, 1466, 1344, 1161, 1089 cm⁻¹.

MS (ESI) m/z 522 (M+H)⁺, 520 (M-H)⁻; ¹H-NMR (DMSO-d₆) δ 8.38 (1H, s), 7.77 (2H, d, J=8.2 Hz), 7.31-7.49 (6H, m), 7.32 (1H, s), 6.53 (1H, br.s), 3.26-3.28 (2H, m), 2.69-2.81 (4H, m), 2.35 (3H, s), 1.25 (3H, t, J=7.6 Hz).

EXAMPLE 319

6-CHLORO-5-(DIMETHYLAMINO)-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. *N*-{6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}-*N,N*-dimethylamine

A mixture of 6-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-ylamine (Example 110, step 6, 100 mg, 0.3 mmol) and NaBH₄ (153 mg, 4 mmol) in THF (5 ml) was added to the mixture of 38% formaldehyde (0.5 ml, 5.6 mmol) and 3M aqueous H₂SO₄ (0.4 ml, 0.12 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h. The reaction mixture was poured into water, and extracted with ethyl acetate (100 ml). The organic layer was washed with brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (1:2) to afford 48 mg (46%) of the title compound as white solids.

MS (EI) m/z: 361 (M⁺).

¹H-NMR (CDCl₃) δ: 7.54 (1H, s), 7.44 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 7.13 (1H, s), 3.82 (2H, t, J=7.0 Hz), 3.19 (2H, t, J=7.0 Hz), 2.82 (6H, s), 2.75 (2H, q, J=7.6 Hz), 1.35 (3H, t, J=7.6 Hz).

STEP 2. *N*-{1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}-*N,N*-dimethylamine

The title compound was prepared according to the procedure described in step 8 of Example 1 from *N*-{6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}-*N,N*-dimethylamine (step 1).

¹H-NMR (CDCl₃) δ: 7.54 (1H, s), 7.43 (2H, d, J=8.2 Hz), 7.29 (2H, d, J=8.2 Hz), 7.12 (1H, s), 3.62 (2H, t, J=7.0 Hz), 3.01 (2H, t, J=7.0 Hz), 2.82 (6H, s), 2.75 (2H, q, J=7.6 Hz), 1.34 (2H, t, J=7.6 Hz).

STEP 3. *N*-{1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}-*N,N*-dimethylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from *N*-{1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}-*N,N*-dimethylamine (step 2).

¹H-NMR (CDCl₃) δ: 7.54 (1H, s), 7.41 (2H, d, J=8.1 Hz), 7.27 (2H, d, J=8.1 Hz), 7.13 (1H, s), 3.08 (2H, t, J=6.9 Hz), 2.87 (2H, t, J=6.9 Hz), 2.82 (6H, s), 2.75 (2H, q, J=7.6 Hz), 1.35 (3H, t, J=7.6 Hz).

STEP 4. 6-chloro-5-(dimethylamino)-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from *N*-{1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}-*N,N*-dimethylamine (step 3).

m.p.: 108-114 °C.

MS (ESI) m/z : 540 (MH⁺), 538 ([M-H]⁻).

¹H-NMR (CDCl₃) δ: 7.73 (2H, d, =8.0 Hz), 7.54 (1H, s), 7.25-7.39 (6H, m), 7.11 (1H, s), 6.73 (1H, br.s), 3.58 (2H, q, J=6.9 Hz), 2.94 (2H, t, J=6.9 Hz), 2.71-2.82 (8H, m), 2.40 (3H, s), 1.33 (3H, t, J=7.6 Hz).

EXAMPLE 320

5 6-CHLORO-2-ETHYL-5-(METHYLAMINO)-1-[4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazol-5-ylformamide

- 10 A solution of acetic anhydride (0.14 ml) in THF (5 ml) was added formic acid (0.06 ml, 1.65 mmol) at 0 °C under nitrogen and the mixture was stirred at 60 °C for 2 h. Then the mixture was recooled to 0 °C and was added 6-Chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazol-5-ylamine(Example 110, step 6, 100 mg, 0.3 mmol) in THF (2 ml). The mixture
- 15 was stirred at room temperature for 2 h. The volatile component was removed under reduced pressure, and the residue was dissolved with ethyl acetate (100 ml). The organic layer was washed with 2N aqueous NaOH (50 ml), brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate
- 20 (1:10) to afford 68 mg (67%) of the title compound as pale yellow solids. MS (EI) m/z: 361 (M⁺).

¹H-NMR (CDCl₃) δ: 8.53-8.76 (1H, br.s), 7.66 (1H, s), 7.44-7.48 (2H, m), 7.26-7.31 (2H, m), 7.18 (1H, s), 3.83 (2H, t, J=6.9 Hz), 3.20 (2H, t, J=6.9 Hz), 2.78 (2H, q, J=7.4 Hz), 1.32-1.39 (3H, m).

25 STEP 2. N-{6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazol-5-yl}-N-methylamine

A solution of (6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl)formamide, step 1, 112 mg, 0.3 mmol) in THF (15 ml) was added Me₂S BH₃ (0.07 ml, 0.77 mmol) under nitrogen at room temperature. The mixture was refluxed for 1 h. Then the mixture was cooled to room temperature and was added methanol (3 ml) and 2*N* aqueous HCl (12 ml). The mixture was stirred at 70 °C for 30 min. The volatile component was removed under reduced pressure, and the residue was dissolved with ethyl acetate (100 ml). The organic layer was washed with saturated aqueous NaHCO₃ (50 ml), brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (1:4) to afford 93 mg (87%) of the title compound as white solids.

MS (EI) *m/z*: 347 (M⁺).

¹H-NMR (CDCl₃) δ: 7.42 (2H, d, J=8.2 Hz), 7.29 (2H, d, J=8.2 Hz), 7.04 (1H, s), 7.03 (1H, s), 3.81 (2H, t, J=6.9 Hz), 3.18 (2H, t, J=6.9 Hz), 2.95 (3H, s), 2.75 (2H, q, J=7.6 Hz), 1.34 (3H, t, J=7.6 Hz).

STEP 3. *N*-{1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}-*N*-methylamine

The title compound was prepared according to the procedure described in step 8 of Example 1 from *N*-{6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}-*N*-methylamine (step 2).

¹H-NMR (CDCl₃) δ: 7.42 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 7.04-7.03 (2H, m), 4.19 (1H, br.s), 3.61 (2H, t, J=7.0 Hz), 3.00 (2H, t, J=7.0 Hz), 2.95 (3H, s), 2.75 (2H, q, J=7.6 Hz), 1.33 (3H, t, J=7.6 Hz).

STEP 4. *N*-{1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}-*N*-methylamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from *N*-{1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}-*N*-methylamine (step 3).

¹H-NMR (CDCl₃) δ: 7.39 (2H, d, J=8.4 Hz), 7.25 (2H, d, J=8.4 Hz), 7.06 (1H, s), 7.03 (1H, s), 3.64 (2H, br.s), 3.15 (2H, t, J=7.2 Hz), 2.94-2.99 (5H, m), 2.73 (2H, q, J=7.5 Hz), 1.32 (3H, t, J=7.5 Hz).

STEP 5. 6-chloro-2-ethyl-5-(methylamino)-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from *N*-{1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl}-*N*-methylamine (step 4).

m.p.: 95-100 °C.

MS (ESI) *m/z* : 526 (MH⁺), 524 ([M-H]⁻).

¹H-NMR (CDCl₃) δ: 7.73 (2H, d, J=8.4 Hz), 7.23-7.36 (7H, m), 7.03 (1H, s), 3.57 (2H, t, J=6.6 Hz), 2.89-2.94 (5H, m), 2.73 (2H, q, J=7.4 Hz), 1.32 (3H, t, J=7.4 Hz).

EXAMPLE 321

4-CYANO-2-ETHYL-1-(4-{2-[(4-

METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE

STEP 1. 3-chloro-2-nitrobenzamide

A mixture of 3-chloro-2-nitro-benzoic acid (1 g, 4.9 mmol) and thionyl chloride (9 ml) was stirred at 80 °C for 1h. The thionyl chloride was removed under reduced pressure, and the residue was dissolved with dichloromethane (15 ml). The mixture was cooled to 0 °C and was added 30% aqueous NH₃ (2 ml) dropwise. The mixture was stirred at 0 °C for 25 min. The reaction mixture was poured into water and extracted with ethyl acetate (300 ml). The organic layer

was washed with saturated aqueous Na_2CO_3 (100 ml), and brine (100 ml). This organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give 1.2 g (quant.) of the title compound as pale orange solids.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.68-7.92 (3H, m).

5 STEP 2. 3-chloro-2-nitrobenzonitrile

A solution of 3-chloro-2-nitrobenzamide (step 1, 1.2 g, 4.9 mmol) in DMF (8 ml) was added thionyl chloride (2 ml, 24.8 mmol) in DMF (3 ml) dropwise at room temperature. The mixture was stirred at 120 °C for 2.5 h. The mixture was poured into ice-water and extracted with ethyl acetate (200 ml).

10 The organic layer was washed with saturated aqueous NaHCO_3 (100 ml), brine (100 ml), then dried (MgSO_4), and concentrated. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (3:1/ 1:2) to give 1 g (quant.) of the title compound as pale yellow solids.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.61-7.68 (1H, m), 7.74-7.78 (2H, m).

15 STEP 3. 2-[4-(3-Cyano-2-nitroanilino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 3-chloro-2-nitrobenzonitrile (step 2) and 4-aminophenylethyl alcohol.

MS (EI) m/z : 283 (M^{+}).

20 $^1\text{H-NMR}$ (CDCl_3) δ : 9.37 (1H, br.s), 7.15-7.41 (7H, m), 3.91 (2H, t, $J=6.4$ Hz), 2.91 (2H, t, $J=6.4$ Hz).

STEP 4. 2-amino-3-[4-(2-hydroxyethyl)anilino]benzonitrile

The title compound was prepared according to the procedure described in step 2 of Example 40 from 2-[4-(3-Cyano-2-nitroanilino)phenyl]ethanol (step 3).

25 MS (EI) m/z : 253 (M^{+}).

¹H-NMR (CDCl₃) δ: 7.22-7.28 (2H, m), 7.10 (2H, d, J=8.4 Hz), 6.69-6.75 (3H, m), 5.13 (1H, br.s), 4.54 (2H, br.s), 3.84 (2H, t, J=6.4 Hz), 2.80 (2H, t, J=6.4 Hz).

STEP 5. 2-[4-(4-cyano-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-amino-3-[4-(2-hydroxyethyl)anilino]benzonitrile (step 4).

TLC, R_f = 0.6, hexane : ethyl acetate (1:1).

STEP 6. 2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazole-4-carbonitrile

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(4-cyano-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate (step 5).

MS (EI) m/z: 291 (M⁺).

¹H-NMR (CDCl₃) δ: 7.58 (1H, d, J=6.3 Hz), 7.49 (2H, d, J=8.3 Hz), 7.19-7.32 (4H, m), 4.01 (2H, t, J=6.4 Hz), 3.02 (2H, t, J=6.4 Hz), 2.86 (2H, q, J=7.6 Hz), 1.34 (3H, t, J=7.6 Hz).

STEP 7. 1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazole-4-carbonitrile

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazole-4-carbonitrile (step 6).

¹H-NMR (DMSO-d₆) δ: 7.72 (1H, dd, J=1.2 Hz, 7.4 Hz), 7.51-7.60 (4H, m), 7.30-7.42 (2H, m), 3.97 (2H, t, J=7.0 Hz), 3.18 (2H, t, J=7.0 Hz), 2.79 (2H, q, J=7.6 Hz), 1.26 (3H, t, J=7.6 Hz).

STEP 8. 1-[4-(2-azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazole-4-carbonitrile

The title compound was prepared according to the procedure described in step 8 of Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazole-4-carbonitrile (step 7).

¹H-NMR (CDCl₃) δ: 7.59 (1H, dd, J=1.2 Hz, 7.3 Hz), 7.48 (2H, d, J=8.0 Hz), 7.19-7.32 (4H, m), 3.63 (2H, t, J=6.6 Hz), 3.03 (2H, t, J=6.6 Hz), 2.84 (2H, q, J=7.6 Hz), 1.31 (3H, t, J=7.6 Hz).

STEP 9. 1-[4-(2-aminoethyl)phenyl]-2-ethyl-1H-benzimidazole-4-carbonitrile

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-2-ethyl-1H-benzimidazole-4-carbonitrile (step 8).

¹H-NMR (CDCl₃) δ: 7.58 (1H, dd, J=1.3 Hz, 7.4 Hz), 7.44 (2H, d, J=8.2 Hz), 7.19-7.32 (4H, m), 3.08 (2H, t, J=6.7 Hz), 2.81-2.93 (4H, m), 1.33 (3H, t, J=7.5 Hz)..

STEP 10. 4-cyano-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-2-ethyl-1H-benzimidazole-4-carbonitrile (step 9).

m.p.: 95-103 °C.

IR (KBr) v: 2225, 1676, 1516, 1433, 1340, 1161, 1091, 794, 663 cm⁻¹.

MS (ESI) m/z : 488 (MH⁺), 486 ([M-H]).

¹H-NMR (CDCl₃) δ: 7.72 (2H, d, J=8.1 Hz), 7.59 (1H, d, J=7.0 Hz), 7.42 (2H, d, J=8.1 Hz), 7.18-7.32 (6H, m), 6.72 (1H, br.s), 3.57 (2H, t, J=7.1 Hz), 2.96 (2H, t, J=7.1 Hz), 2.85 (2H, q, J=7.6 Hz), 2.41 (3H, s), 1.33 (3H, t, J=7.6 Hz).

EXAMPLE 322

2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-1H-BENZIMIDAZOLE-4-CARBOXAMIDE

STEP 1. 2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole-4-carboxamide

To a stirred suspension of 2-{4-[(3-amino-4,6-dimethyl-2-pyridinyl)amino]phenyl}ethanol (step 4, 820 mg, 3.3 mmol) in toluene (30 ml) was added dropwise propionyl chloride (630 mg, 6.8 mmol) at 0 °C, and the reaction mixture was refluxed for 1.5 h. After cooling, the mixture was poured into water (50 ml) and extracted with ethyl acetate (100 ml). The organic layer was washed with 2N aqueous NaOH (50 ml) and brine (50 ml), then dried (Na₂SO₄). The solvent was removed under reduced pressure and the residue was dissolved with THF (20 ml) and methanol (20 ml). The mixture was added 4N aqueous LiOH (10 ml) and stirred at room temperature for 14 h. The mixture was evaporated. The residue was dissolved with ethyl acetate (100 ml) and washed with water (50 ml). The organic layer was washed with brine (50 ml), and dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (1:2 / 1:5 / 0:1) to afford 260 mg (26%) of the title compound as white solids.

MS (EI) m/z: 309 (M⁺).

¹H-NMR (CDCl₃) δ: 9.81 (1H, br.s), 8.13 (1H, dd, J=2.0 Hz, 7.0 Hz), 7.47 (2H, d, J=8.0 Hz), 7.25-7.31 (4H, m), 5.99 (1H, br.s), 4.00 (2H, t, J=6.4 Hz), 3.01 (2H, t, J=6.4 Hz), 2.82 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz).

STEP 2. 1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazole-4-carboxamide

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-(6-chloro-2-ethyl-5-nitro-1H-benzimidazol-1-yl)phenyl]ethanol (step 1).

¹H-NMR (DMSO-d₆) δ: 9.29 (1H, br.s), 7.81-7.91 (1H, m), 7.79 (1H, br.s), 7.49-7.60 (4H, m), 7.24-7.33 (2H, m), 3.97 (2H, t, J=6.8 Hz), 3.18 (2H, t, J=6.8 Hz), 2.80 (2H, q, J=7.5 Hz), 1.27 (3H, t, J=7.5 Hz).

STEP 3. 1-[4-(2-azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazole-4-carboxamide

The title compound was prepared according to the procedure described in step 8 of Example 1 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazole-5-carboxamide (step 2).

¹H-NMR (DMSO-d₆) δ: 9.29 (1H, br.s), 7.89 (1H, d, J=7.3 Hz), 7.79 (1H, br.s), 7.51-7.59 (4H, m), 7.22-7.33 (2H, m), 3.68 (2H, t, J=6.6 Hz), 3.01 (2H, t, J=6.6 Hz), 2.77 (2H, q, J=7.5 Hz), 1.27 (3H, t, J=7.5 Hz).

STEP 4. 1-[4-(2-aminoethyl)phenyl]-2-ethyl-1*H*-benzimidazole-4-carboxamide

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazole-5-carboxamide (step 3).

¹H-NMR (DMSO-d₆) δ: 9.30 (1H, br.s), 7.89 (1H, d, J=6.5 Hz), 7.81 (1H, br.s), 7.48-7.49 (4H, m), 7.26-7.30 (2H, m), 2.77-2.89 (6H, m), 1.28 (3H, t, J=6.4 Hz).

STEP 5. 2-ethyl-1-[4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl]amino}ethyl]phenyl]-1*H*-benzimidazole-4-carboxamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazole-5-carboxamide (step 4).

m.p.: 208-214 °C.

IR (KBr) ν: 3336, 1664, 1589, 1508, 1406, 1342, 1168, 976 cm⁻¹.

MS (ESI) m/z : 506 (MH⁺), 504 ([M-H]).

¹H-NMR (DMSO-d₆) δ: 9.29 (1H, br.s), 7.89 (1H, dd, J=1.3 Hz, 7.2 Hz), 7.75-7.79 (3H, m), 7.22-7.49 (8H, m), 6.54 (1H, br.s), 2.75-2.83 (4H, m), 2.35 (3H, s), 1.27 (3H, t, J=7.4 Hz).

EXAMPLE 323

5 6-CHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-5-(METHYLSULFONYL)-1H-BENZIMIDAZOLE

STEP 1. 1,5-dichloro-2-(methylsulfinyl)-4-nitrobenzene

- A mixture of (2,4-dichloro-phenyl)-methyl sulfone (Ono Mitsunori,
10 Nakamura Yoshisada, Sato Shingo, Itoh Isamu, *Chem. Lett*, 1988, 395-398.; 3.33 g, 16 mmol) and sulfuric acid (conc, 14 ml) was added a mixture of sulfuric acid (4 ml) and nitric acid (fuming, 2 ml) dropwise under ice-water bath. The mixture was stirred at 55 °C for 1 h. The mixture was poured onto ice-water and neutralized with 6N aqueous NaOH and then extracted with dichloromethane.
15 The organic layer was washed with brine and dried (Na₂SO₄). The solvent was removed under reduced pressure and the residue was purified by flash chromatography eluting with hexane/ethyl acetate (2:1/ 1:1) to give 3 g (74%) of the title compound as white solids.

¹H-NMR (CDCl₃) δ: 8.45 (1H, s), 7.65 (1H, s), 2.89 (3H, s).

20 STEP 2. 1,5-dichloro-2-(methylsulfonyl)-4-nitrobenzene

- A solution of 1,5-dichloro-2-(methylsulfinyl)-4-nitrobenzene (1.0 g, 3.9 mmol) in dichloromethane (50 ml) was added 3-Chloroperoxybenzoic acid (1.7 g, 9.8 mmol). The mixture was stirred under nitrogen at room temperature for 3 h. The mixture was added saturated aqueous NaHCO₃ (20 ml) and extracted
25 with dichloromethane (50 ml). The organic layer was washed with brine (50 ml), dried (Na₂SO₄) and concentrated. The residue was purified by flash

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chromatography eluting with hexane/ethyl acetate (2:1) to give 1 g (100%) of the title compound as white solids.

MS (EI) m/z : 269 (M^+).

$^1\text{H-NMR}$ (CDCl_3) δ : 8.68 (1H, s), 7.81 (1H, s), 3.30 (3H, s).

5 STEP 3. 2-{4-[5-chloro-4-(methylsulfonyl)-2-nitroanilino]phenyl}ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 1,5-dichloro-2-(methylsulfonyl)-4-nitrobenzene and 4-aminophenylethyl alcohol (step 2).

MS (EI) m/z : 370 (M^+)

10 $^1\text{H-NMR}$ (CDCl_3) δ : 9.81 (1H, br.s), 8.99 (1H, s), 7.39 (2H, d, $J=8.4$ Hz), 7.24 (2H, d, $J=8.4$ Hz), 7.18 (1H, s), 3.94 (2H, t, $J=6.2$ Hz), 3.25 (3H, s), 2.95 (2H, t, $J=6.2$ Hz).

STEP 4. 2-{4-[2-amino-5-chloro-4-(methylsulfonyl)anilino]phenyl}ethanol

15 The title compound was prepared according to the procedure described in step 2 of Example 40 from 2-{4-[5-chloro-4-(methylsulfonyl)-2-nitroanilino]phenyl}ethanol (step 3).

MS (EI) m/z : 340 (M^+)

20 $^1\text{H-NMR}$ (CDCl_3) δ : 7.50 (1H, s), 7.22 (2H, d, $J=8.4$ Hz), 7.15 (1H, s), 7.00 (2H, d, $J=8.4$ Hz), 5.71 (1H, br.s), 3.88 (2H, t, $J=6.4$ Hz), 3.67 (2H, br.s), 3.22 (3H, s), 2.86 (2H, t, $J=6.4$ Hz).

STEP 5. 2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethyl propionate

25 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[2-amino-5-chloro-4-(methylsulfonyl)anilino]phenyl}ethanol (step 4).
TLC, $R_f = 0.7$, hexane : ethyl acetate (1:2).

STEP 6. 2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-

- 5 benzimidazol-1-yl]phenyl}ethyl propionate (step 5).

MS (EI) m/z: 378 (M⁺)

¹H-NMR (CDCl₃) δ: 8.60 (1H, s), 7.52 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 7.10 (1H, s), 3.97-4.04 (2H, m), 3.29 (3H, s), 3.03 (2H, t, J=6.5 Hz), 2.80 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

- 10 STEP 7. 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazol-5-yl methyl sulfone

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethanol (step 6).

- 15 ¹H-NMR (CDCl₃) δ: 8.62 (1H, s), 7.50 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 7.24 (1H, s), 3.83 (2H, t, J=7.1 Hz), 3.29 (3H, s), 3.22 (2H, t, J=7.1 Hz), 2.80 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz).

STEP 8. 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1H-benzimidazol-5-yl methyl sulfone

- 20 The title compound was prepared according to the procedure described in step 8 of Example 1 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazol-5-yl methyl sulfone (step 7).

- ¹H-NMR (CDCl₃) δ: 8.62 (1H, s), 7.50 (2H, d, J=8.4 Hz), 7.25 (2H, d, J=8.4 Hz), 7.23 (1H, s), 3.64 (2H, t, J=6.9 Hz), 3.29 (3H, s), 3.04 (2H, t, J=6.9 Hz), 2.80 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

STEP 9. 2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethanamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-1*H*-benzimidazol-5-yl methyl sulfone (step 8).

¹H-NMR (CDCl₃) δ: 8.61 (1H, s), 7.47 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 7.24 (1H, s), 3.29 (3H, s), 3.10 (2H, t, J=7.1 Hz), 2.90 (2H, t, J=7.1 Hz), 2.80 (2H, q, J=7.5 Hz), 1.37 (3H, t, J=7.5 Hz).

STEP 10. 6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-5-(methylsulfonyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1*H*-benzimidazol-1-yl]phenyl}ethanamine (step 9).

m.p.: 105-118 °C.

IR (KBr) v: 2879, 1676, 1518, 1458, 1309, 1142, 1089, 993 cm⁻¹.

MS (ESI) m/z : 575 (MH⁺), 573 ([M-H]⁻).

¹H-NMR (CDCl₃) δ: 8.59 (1H, s), 7.75 (2H, d, J=8.4 Hz), 7.43 (2H, d, J=8.4 Hz), 7.29-7.33 (4H, m), 7.21 (1H, s), 6.69 (1H, br.s), 3.55-3.62 (2H, m), 3.29 (3H, s), 2.96 (2H, t, J=6.9 Hz), 2.80 (3H, q, J=7.5 Hz), 2.41 (3H, s), 1.34 (3H, t, J=7.5 Hz).

EXAMPLE 324

6-CHLORO-2-ETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO}ETHYL}PHENYL)-5-(METHYLSULFONYL)-1*H*-BENZIMIDAZOLE SODIUM SALT

The title compound was prepared according to the procedure described in Example 2 from 6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-5-(methylsulfonyl)-1*H*-benzimidazole (Example 323)

m.p.: 175-183 °C.

IR (KBr) ν : 3375, 1604, 1516, 1458, 1139, 1083, 993 cm^{-1} .

EXAMPLE 325

2-{4-[6-CHLORO-2-ETHYL-5-(METHYLSULFONYL)-1H-

- 5 BENZIMIDAZOL-1-YL]PHENYL} ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

- The title compound was prepared according to the procedure described
10 in Example 3 from 2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl} ethanol (Example 323, step 6).

m.p.: 105-110 °C.

IR (KBr) ν : 1751, 1517, 1458, 1309, 1163, 1141, 1089 cm^{-1} .

MS (ESI) m/z : 576 (MH^+), 574 ($[\text{M}-\text{H}]^-$).

- 15 $^1\text{H-NMR}$ (CDCl_3) δ : 8.60 (1H, s), 7.91-7.94 (2H, m), 7.21-7.43 (7H, m), 4.40 (2H, br.s), 3.31 (3H, s), 3.05 (2H, br.s), 2.78-2.81 (2H, m), 2.44 (3H, s), 1.33 (3H, t, $J=7.6$ Hz).

EXAMPLE 326

5-(AMINOSULFONYL)-6-CHLORO-2-ETHYL-1-(4-{2-[(4-

- 20 METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE

STEP 1. 2,4-dichloro-5-nitrobenzenesulfonyl chloride

- 2,4-Dichloronitrobenzene (10 g, 52 mmol) was added ClSO_3H (8 ml, 120 mmol) dropwise under ice-water bath. The mixture was stirred at 130 °C
25 for 26 h. The mixture was cooled to rt and poured onto ice-water. The resulting precipitates were collected by filtration and dried under reduced pressure to give 9 g (60%) of the title compound as brown solids.

MS (EI) m/z: 290 (M⁺)

¹H-NMR (CDCl₃) δ: 8.70 (1H, s), 7.90 (1H, s).

STEP 2. *N*-(*tert*-butyl)-2,4-dichloro-5-nitrobenzenesulfonamide

The title compound was prepared according to the procedure described in step 1 of Example 87 from 2,4-dichloro-5-nitrobenzenesulfonyl chloride and *tert*-butylamine (step 1).

¹H-NMR (CDCl₃) δ: 8.65 (1H, s), 7.74 (1H, s), 5.01 (1H, br.s), 1.27 (9H, s).

STEP 3. *N*-(*tert*-butyl)-2-chloro-4-[4-(2-hydroxyethyl)anilino]-5-nitrobenzenesulfonamide

The title compound was prepared according to the procedure described in step 1 of Example 162 from *N*-(*tert*-butyl)-2,4-dichloro-5-nitrobenzenesulfonamide and 4-aminophenylethyl alcohol (step 2).

¹H-NMR (CDCl₃) δ: 9.72 (1H, br.s), 8.95 (1H, s), 7.37 (2H, d, J=8.3 Hz), 7.24 (2H, d, J=8.3 Hz), 7.17 (1H, s), 4.79 (1H, br.s), 3.90-3.96 (2H, m), 2.94 (2H, t, J=6.4 Hz), 1.26 (9H, s).

STEP 4. 5-amino-*N*-(*tert*-butyl)-2-chloro-4-[4-(2-hydroxyethyl)anilino]benzenesulfonamide

The title compound was prepared according to the procedure described in step 2 of Example 40 from *N*-(*tert*-butyl)-2-chloro-4-[4-(2-hydroxyethyl)anilino]-5-nitrobenzenesulfonamide (step 3).

MS (EI) m/z: 397(M⁺)

¹H-NMR (CDCl₃) δ: 7.51 (1H, s), 7.20 (2H, d, J=8.4 Hz), 7.14 (1H, s), 6.95 (2H, d, J=8.4 Hz), 5.22 (1H, br.s), 4.89 (1H, br.s), 3.87 (2H, t, J=6.4 Hz), 2.85 (2H, t, J=6.4 Hz), 1.23 (9H, s).

STEP 5. 2-[4-(6-Chloro-2-ethyl-5-nitro-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 5-amino-*N*-(*tert*-butyl)-2-chloro-4-[4-(2-hydroxyethyl)anilino]benzenesulfonamide (step 4).

TLC, R_f = 0.8, hexane : ethyl acetate (1:2).

5 STEP 6. *N*-(*tert*-butyl)-6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazole-5-sulfonamide

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(6-Chloro-2-ethyl-5-nitro-1*H*-benzimidazol-1-yl)phenyl]ethyl propionate (step 5).

10 ¹H-NMR (CDCl₃) δ: 8.57 (1H, s), 7.49 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.20 (1H, s), 4.98 (1H, br.s), 4.00 (2H, br.s), 3.02 (2H, t, J=6.4 Hz), 2.79 (2H, q, J=7.5 Hz), 1.37 (3H, t, J=7.5 Hz), 1.21 (9H, s).

STEP 7. *N*-(*tert*-butyl)-6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazole-5-sulfonamide

15 The title compound was prepared according to the procedure described in step 7 of Example 1 from *N*-(*tert*-butyl)-6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazole-5-sulfonamide (step 6).

¹H-NMR (CDCl₃) δ: 8.58 (1H, s), 7.49 (2H, d, J=8.4 Hz), 7.32 (2H, d, J=8.4 Hz), 7.19 (1H, s), 4.96 (1H, br.s), 3.83 (2H, t, J=7.0 Hz), 3.21 (2H, t, J=7.0 Hz),
20 2.80 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz), 1.22 (9H, s).

STEP 8. 1-[4-(2-azidoethyl)phenyl]-*N*-(*tert*-butyl)-6-chloro-2-ethyl-1*H*-benzimidazole-5-sulfonamide

The title compound was prepared according to the procedure described in step 8 of Example 1 from *N*-(*tert*-butyl)-6-chloro-1-[4-(2-chloroethyl)phenyl]-

25 2-ethyl-1*H*-benzimidazole-5-sulfonamide (step 7).

¹H-NMR (CDCl₃) δ: 8.57 (1H, s), 7.48 (2H, d, J=8.2 Hz), 7.32 (2H, d, J=8.2 Hz), 7.19 (1H, s), 4.96 (1H, br.s), 3.63 (2H, t, J=6.9 Hz), 3.03 (2H, t, J=6.9 Hz), 2.79 (2H, q, J=7.4 Hz), 1.37 (3H, t, J=7.4 Hz), 1.21 (9H, s).

STEP 9. 1-[4-(2-aminoethyl)phenyl]-N-(tert-butyl)-6-chloro-2-ethyl-1H-

5 benzimidazole-5-sulfonamide

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-N-(tert-butyl)-6-chloro-2-ethyl-1H-benzimidazole-5-sulfonamide (step 8).

¹H-NMR (CDCl₃) δ: 8.57 (1H, s), 7.44 (2H, d, J=8.5 Hz), 7.29 (2H, d, J=8.5 Hz), 7.20 (1H, s), 5.03 (1H, br.s), 3.09 (2H, t, J=6.9 Hz), 2.89 (2H, t, J=6.9 Hz), 2.79 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz), 1.22 (9H, s).

STEP 10. 5-[(tert-butylamino)sulfonyl]-6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole

15 The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-N-(tert-butyl)-6-chloro-2-ethyl-1H-benzimidazole-5-sulfonamide (step 9).

¹H-NMR (CDCl₃) δ: 8.54 (1H, s), 7.78 (2H, d, J=8.3 Hz), 7.41 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=8.2 Hz), 7.23 (2H, d, J=8.2 Hz), 7.16 (1H, s), 6.61 (1H, br.s), 5.21 (1H, br.s), 3.54-3.60 (2H, m), 2.95 (2H, t, J=6.9 Hz), 2.78 (2H, q, J=7.5 Hz), 2.41 (3H, s), 1.35 (3H, t, J=7.5 Hz), 1.21 (9H, s).

STEP 11. 5-(aminosulfonyl)-6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole

25 The title compound was prepared according to the procedure described in step 1 of Example 88 from 5-[(tert-butylamino)sulfonyl]-6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole (step 9).

m.p.: 163-170 °C.

IR (KBr) ν : 1676, 1517, 1400, 1340, 1159, 1089, 995 cm^{-1} .

MS (ESI) m/z : 576 (MH^+), 574 ($[\text{M}-\text{H}]^-$).

^1H -NMR ($\text{DMSO}-d_6$) δ : 8.25 (1H, s), 7.77 (2H, d, $J=8.3$ Hz), 7.55 (2H, br.s), 7.37-7.48 (6H, m), 7.20 (1H, s), 6.54 (1H, br.s), 3.27 (2H, br.s), 2.71-2.81 (4H, m), 2.34 (3H, s), 1.23 (3H, t, $J=7.6$ Hz).

EXAMPLE 327

2-{4-[5-(AMINOSULFONYL)-6-CHLORO-2-ETHYL-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 2-(4-{5-[(*tert*-butylamino)sulfonyl]-6-chloro-2-ethyl-1*H*-benzimidazol-

1-yl}phenyl)ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from *N*-(*tert*-butyl)-6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazole-5-sulfonamide (Example 326, step 6).

^1H -NMR (CDCl_3) δ : 8.58 (1H, s), 7.93 (2H, d, $J=8.2$ Hz), 7.33-7.39 (4H, m), 7.20 (2H, d, $J=8.2$ Hz), 7.16 (1H, s), 5.07 (1H, br.s), 4.38 (2H, t, $J=6.2$ Hz), 3.03 (2H, t, $J=6.2$ Hz), 2.78 (2H, q, $J=7.5$ Hz), 2.44 (3H, s), 1.35 (3H, t, $J=7.5$ Hz), 1.21 (9H, s).

STEP 2. 2-{4-[5-(aminosulfonyl)-6-chloro-2-ethyl-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in step 1 of Example 88 from 2-(4-{5-[(*tert*-butylamino)sulfonyl]-6-chloro-2-ethyl-1*H*-benzimidazol-1-yl}phenyl)ethyl (4-methylphenyl)sulfonylcarbamate (step 1).

m.p.: 110-115 $^\circ\text{C}$.

IR (KBr) ν : 1676, 1517, 1400, 1340, 1159, 1089, 995 cm^{-1} .

MS (ESI) m/z : 576 (MH^+), 574 ($[\text{M}-\text{H}]^-$).

¹H-NMR (DMSO-d₆) δ: 8.25 (1H, s), 7.76 (2H, d, J=8.4 Hz), 7.55 (2H, br.s), 7.47 (4H, s), 7.41 (2H, d, J=8.4 Hz), 7.20 (1H, s), 4.29 (2H, t, L=6.6 Hz), 2.96 (2H, t, J=6.6 Hz), 2.75 (2H, q, J=7.5 Hz), 2.35 (3H, s), 1.24 (3H, t, J=7.5 Hz).

EXAMPLE 328

- 5 2-[4-(6-CHLORO-5-CYANO-2-ETHYL-1*H*-BENZIMIDAZOL-1-
YL)PHENYL]ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 2-[4-(6-chloro-5-cyano-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl(4-
methylphenyl)sulfonylcarbamate

- 10 The title compound was prepared according to the procedure described
in Example 3 from 6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-
benzimidazole-5-carbonitrile (Example 111, step 4).

m.p.: 85-98 °C.

IR (KBr) v: 1747, 1618, 1517, 1465, 1348, 1290, 1163, 1089 cm⁻¹

MS (ESI) m/z: 523 (MH⁺), 521 ([M-H]⁻)

- 15 ¹H-NMR (CDCl₃) δ: 8.07 (1H, s), 7.92 (2H, d, J=8.4 Hz), 7.40 (2H, d, J=8.4
Hz), 7.35 (2H, d, J=8.1 Hz), 7.25 (2H, d, J=8.1 Hz), 7.17 (1H, s), 4.39 (2H, t,
J=6.8 Hz), 3.04 (2H, t, J=6.8 Hz), 2.78 (2H, q, J=7.6 Hz), 2.44 (3H, s), 1.35 (3H,
t, J=7.6 Hz).

EXAMPLE 329

- 20 N-[(2-[4-(5-CYANO-2-ETHYL-4,6-DIMETHYL-1*H*-BENZIMIDAZOL-1-
YL)PHENYL]ETHYL)AMINO)CARBONYL]-4-
METHYLBENZENESULFONAMIDE
STEP 1. 4-cyano-3,5-dimethyl-2-nitrophenyl trifluoromethanesulfonate

- 25 To a solution of 4-hydroxy-2,6-dimethyl-3-nitro-benzonitrile (v.Auwers;
Saurwein; Fortsch. Ch. Phys.; 18; Heft 2, S. 23; 2.6 g, 13.4 mmol) in
dichloromethane (150 ml) was added triflic anhydride (3.4 ml, 20 mmol) and
pyridine (1.5 ml, 20 mmol) at 0 °C. The mixture was stirred at room

temperature for 1.5 h. The reaction mixture was poured into water, and extracted with ethyl acetate (100 ml). The organic layer was washed with brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (2:1)

to afford 3 g (69%) of the title compound as pale yellow solids.

MS (EI) m/z: 324 (M⁺)

¹H-NMR (CDCl₃) δ: 7.34 (1H, s), 2.68 (3H, s), 2.61 (3H, s).

STEP 2. 2-{4-[(4-cyano-3,5-dimethyl-2-nitrophenyl)amino]phenyl}ethyl acetate

The title compound was prepared according to the procedure described in step 3 of Example 1 from 4-cyano-3,5-dimethyl-2-nitrophenyl trifluoromethanesulfonate (step 1).

¹H-NMR (CDCl₃) δ: 8.08 (1H, br.s), 7.27 (2H, d, J=8.4 Hz), 7.15 (2H, d, J=8.4 Hz), 4.30 (2H, t, J=7.0 Hz), 2.96 (2H, t, J=7.0 Hz), 2.65 (3H, s), 2.41 (3H, s), 2.05 (3H, s).

STEP 3. 2-{4-[(4-cyano-3,5-dimethyl-2-nitrophenyl)amino]phenyl}ethyl acetate

The title compound was prepared according to the procedure described in step 3 of Example 6 from 2-{4-[(4-cyano-3,5-dimethyl-2-nitrophenyl)amino]phenyl}ethyl acetate (step 2).

¹H-NMR (CDCl₃) δ: 7.14 (2H, d, J=8.4 Hz), 6.85-6.89 (3H, m), 5.50 (1H, br.s), 4.26 (2H, t, J=7.1 Hz), 3.54 (2H, br.s), 2.89 (2H, t, J=7.1 Hz), 2.41 (3H, s), 2.37 (3H, s), 2.05 (3H, s).

STEP 4. 2-{4-(5-cyano-2-ethyl-4,6-dimethyl-1H-benzimidazol-1-yl)phenyl}ethyl acetate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(4-cyano-3,5-dimethyl-2-nitrophenyl)amino]phenyl}ethyl acetate (step 3).

¹H-NMR (CDCl₃) δ: 7.45-7.47 (2H, m), 7.26-7.29 (2H, m), 6.79 (1H, br.s), 4.37 (2H, t, J=7.0 Hz), 3.08 (2H, t, J=7.0 Hz), 2.83-2.89 (5H, m), 2.56 (3H, s), 2.09 (3H, s), 1.28 (3H, br.s).

STEP 5. 2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-4,6-dimethyl-1H-benzimidazole-

5 5-carbonitrile

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5-cyano-2-ethyl-4,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl acetate (step 4).

MS (EI) m/z: 319 (M⁺)

10 ¹H-NMR (CDCl₃) δ: 7.40-7.51 (4H, m), 6.93 (1H, s), 3.68-3.75 (2H, m), 2.85 (2H, t, J=6.7 Hz), 2.68-2.76 (5H, m), 2.50 (3H, s), 1.22 (3H, t, J=7.4 Hz).

STEP 6. 1-[4-(2-chloroethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carbonitrile

15 The title compound was prepared according to the procedure described in step 7 Example 1 from 2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-4,6-dimethyl-1H-benzimidazole-5-carbonitrile (step 5).

¹H-NMR (CDCl₃) δ: 7.45 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz), 6.79 (1H, s), 3.83 (2H, t, J=7.1 Hz), 3.21 (2H, t, J=7.1 Hz), 2.88 (3H, s), 2.81 (2H, q, J=7.6 Hz), 2.55 (3H, s), 1.29 (3H, t, J=7.6 Hz).

20 STEP 7. 1-[4-(2-azidoethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carbonitrile

The title compound was prepared according to the procedure described in step 8 Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carbonitrile (step 6).

25 MS (EI) m/z: 412 (M⁺)

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¹H-NMR (CDCl₃) δ: 7.47 (2H, d, J=8.1 Hz), 7.28 (2H, d, J=8.1 Hz), 6.78 (1H, s), 3.63 (2H, t, J=6.8 Hz), 3.03 (2H, t, J=6.8 Hz), 2.87 (3H, s), 2.80 (2H, q, J=7.6 Hz), 2.55 (3H, s), 1.29 (3H, t, J=7.6 Hz).

STEP 8. 1-[4-(2-aminoethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carbonitrile

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carbonitrile (step 7).

¹H-NMR (CDCl₃) δ: 7.43 (2H, d, J=8.6 Hz), 7.25 (2H, d, J=8.6 Hz), 6.79 (1H, s), 3.08 (2H, t, J=7.0 Hz), 2.63-2.91 (7H, m), 2.55 (3H, s), 1.29 (3H, t, J=7.6 Hz).

STEP 9. N-[(2-[4-(5-cyano-2-ethyl-4,6-dimethyl-1H-benzimidazol-1-yl)phenyl]ethyl)amino]carbonyl]-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carbonitrile (step 8).

m.p.: 140-145 °C.

IR (KBr) ν: 3340, 2214, 1664, 1517, 1338, 1166, 1091 cm⁻¹

MS (ESI) m/z: 516 (MH⁺), 514 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 7.71 (2H, d, J=8.4 Hz), 7.41 (2H, d, J=8.4 Hz), 7.25-7.31 (4H, m), 6.77 (1H, s), 6.73 (1H, br.s), 3.55-3.62 (2H, m), 2.95 (2H, t, J=7.0 Hz), 2.87 (3H, s), 2.80 (2H, q, J=7.6 Hz), 2.52 (3H, s), 2.41 (3H, s), 1.28 (3H, t, J=7.6 Hz).

EXAMPLE 330

2-{4-[5-(AMINOCARBONYL)-6-CHLORO-2-ETHYL-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

step 1. 2-[4-[5-(aminocarbonyl)-6-chloro-2-ethyl-1*H*-benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-

5 benzimidazole-5-carboxamide (Example 111, step 5)

m.p.: 170-175 °C.

IR (KBr) ν : 3463, 3342, 1747, 1685, 1593, 1161, 1080, 881 cm^{-1}

MS (ESI) m/z : 541 (MH^+), 539 ($[\text{M}-\text{H}]^-$)

$^1\text{H-NMR}$ (CDCl_3) δ : 8.13 (1H, s), 7.96 (2H, d, $J=8.4$ Hz), 7.40 (2H, d, $J=8.4$ Hz), 7.36 (2H, d, $J=8.1$ Hz), 7.01 (2H, d, $J=8.1$ Hz), 6.94 (1H, s), 6.55 (1H, br.s), 4.38 (2H, t, $J=6.1$ Hz), 3.01 (2H, t, $J=6.1$ Hz), 2.70 (2H, q, $J=7.5$ Hz), 2.45 (3H, s), 1.29 (3H, t, $J=7.5$ Hz).

EXAMPLE 331

2-[4-(5-CYANO-2-ETHYL-4,6-DIMETHYL-1*H*-BENZIMIDAZOL-1-YL)PHENYL]ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE
15 step 1. 2-[4-(5-cyano-2-ethyl-4,6-dimethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl(4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-4,6-dimethyl-1*H*-

20 benzimidazole-5-carbonitrile (Example 329, step 5)

m.p.: 208-213 °C.

IR (KBr) ν : 1747, 1517, 1230, 1161, 1089 cm^{-1}

MS (ESI) m/z : 517 (MH^+), 515 ($[\text{M}-\text{H}]^-$)

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 7.76 (2H, d, $J=8.4$ Hz), 7.40-7.48 (6H, m), 6.91 (1H, s), 4.27 (2H, t, $J=6.7$ Hz), 2.96 (2H, t, $J=6.7$ Hz), 2.67-2.73 (5H, m), 2.48 (3H, s), 2.36 (3H, s), 1.21 (3H, t, $J=7.6$ Hz).

EXAMPLE 332

2-[4-(5-ACETYL-2-ETHYL-1H-BENZIMIDAZOL-1-YL)PHENYL]ETHYL
(4-METHYLPHENYL)SULFONYLCARBAMATE
step 1. 2-[4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl (4-
methylphenyl)sulfonylcarbamate

- 5 The title compound was prepared according to the procedure described
in Example 3 from 1-{2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazol-
5-yl}ethanone (Example 78, step 4)

m.p.: 188-190 °C.

IR (KBr) v: 1743, 1683, 1606, 1515, 1348, 1163, 1076 cm⁻¹

- 10 MS (ESI) m/z: 506 (MH⁺), 504 ([M-H]⁻)

¹H-NMR (DMSO-d₆) δ: 8.33 (1H, d, J=1.4 Hz), 7.82 (1H, dd, J=1.4 Hz, 8.4 Hz),
7.76 (2H, d, J=8.4 Hz), 7.45 (4H, s), 7.40 (2H, d, J=8.4 Hz), 7.14 (1H, d, J=8.4
Hz), 4.28 (2H, t, J=6.5 Hz), 2.97 (2H, t, J=6.5 Hz), 2.75 (2H, q, J=7.4 Hz), 2.64
(3H, s), 2.35 (3H, s), 1.25 (3H, t, J=7.4 Hz).

- 15 EXAMPLE 333

6-CHLORO-2-ETHYL-N-METHYL-1-(4-{2-[(4-
METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PH
ENYL)-1H-BENZIMIDAZOLE-5-CARBOXAMIDE
STEP 1. 2,4-dichloro-N-methyl-5-nitrobenzamide

- 20 To a solution of 2,4-dichloro-5-nitrobenzoic acid (8 g, 33.9 mmol) in
toluene (200 ml) was added thionyl chloride (12.4 ml, 169 mmol) at room
temperature. The mixture was stirred at 80 °C for 5 h. The solvent was
removed and the residue was dissolved with tetrahydrofuran (60 ml). The
mixture was added 40% methylamine (1.4 ml, 33.9 mmol) at 0 °C and the
25 mixture was stirred at room temperature for 2.5 h. The volatile component was
removed under reduced pressure, and the residue was extracted with ethyl
acetate (100 ml). The organic layer was washed with water (100 ml), brine (100

ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (2:1/1:1/1:2) to afford 5.3 g (63%) of the title compound as pale yellow solids.

¹H-NMR (CDCl₃) δ: 8.27 (1H, s), 7.65 (1H, s), 3.15 (3H, s).

5 STEP 2. 2-chloro-4-{{[4-(2-hydroxyethyl)phenyl]amino}-N-methyl-5-nitrobenzamide}

The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4-dichloro-N-methyl-5-nitrobenzamide (step 1).

¹H-NMR (CDCl₃) δ: 9.62 (1H, s), 8.22 (1H, s), 7.24-7.35 (4H, m), 6.95 (1H, s), 3.60-3.67 (2H, m), 2.73-2.79 (5H, m).

10 STEP 3. 5-amino-2-chloro-4-{{[4-(2-hydroxyethyl)phenyl]amino}-N-methylbenzamide}

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-chloro-4-{{[4-(2-hydroxyethyl)phenyl]amino}-N-methyl-5-nitrobenzamide (step 2).

¹H-NMR (CDCl₃) δ: 7.28 (1H, s), 7.15 (2H, d, J=8.4 Hz), 7.08 (1H, s), 6.89 (2H, d, J=8.4 Hz), 6.53 (1H, br.s), 5.41 (1H, br.s), 3.84-3.86 (2H, m), 3.66 (2H, br.s), 3.00 (3H, d, J=5.0 Hz), 2.83 (2H, t, J=6.6 Hz).

20 STEP 4. 6-chloro-2-ethyl-1-{{[4-(2-hydroxyethyl)phenyl]-N-methyl-1H-benzimidazole-5-carboxamide}

The title compound was prepared according to the procedure described in step 5 of Example 1 from 5-amino-2-chloro-4-{{[4-(2-hydroxyethyl)phenyl]amino}-N-methylbenzamide (step 3).

MS (EI) m/z: 357 (M⁺)

25 ¹H-NMR (CDCl₃) δ: 7.98 (1H, s), 7.47 (2H, d, J=8.1 Hz), 7.27 (2H, d, J=8.1 Hz), 7.09 (1H, s), 6.23 (1H, br.s), 3.96-4.02 (2H, m), 3.05 (3H, d, J=4.9 Hz), 3.00 (2H, t, J=6.4 Hz), 2.77 (2H, q, J=7.6 Hz), 1.34 (3H, t, J=7.6 Hz).

STEP 5. 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-N-methyl-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 7 Example 1 from 6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-N-

- 5 methyl-1H-benzimidazole-5-carboxamide (step 4).

$^1\text{H-NMR}$ (CDCl_3) δ : 7.98 (1H, s), 7.47 (2H, d, $J=8.3$ Hz), 7.31 (2H, d, $J=8.3$ Hz), 7.10 (1H, s), 6.35 (1H, br.s), 3.83 (2H, t, $J=6.9$ Hz), 3.21 (2H, t, $J=6.9$ Hz), 3.05 (3H, d, $J=4.9$ Hz), 2.82 (2H, q, $J=7.6$ Hz), 1.36 (3H, t, $J=7.6$ Hz).

STEP 6. 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-N-methyl-1H-benzimidazole-5-carboxamide

- 10

The title compound was prepared according to the procedure described in step 8 Example 1 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-ethyl-N-methyl-1H-benzimidazole-5-carboxamide (step 5).

MS (EI) m/z : 382 (M $^+$)

- 15 $^1\text{H-NMR}$ (CDCl_3) δ : 7.94 (1H, s), 7.46 (2H, d, $J=8.0$ Hz), 7.27 (2H, d, $J=8.0$ Hz), 7.06 (1H, s), 3.63 (2H, t, $J=7.0$ Hz), 2.98-3.06 (5H, m), 2.77 (2H, q, $J=7.5$ Hz), 1.34 (3H, t, $J=7.6$ Hz).

STEP 7. 1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-N-methyl-1H-benzimidazole-5-carboxamide

- 20 The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-N-methyl-1H-benzimidazole-5-carboxamide (step 6).

- 25 $^1\text{H-NMR}$ (CDCl_3) δ : 7.91 (1H, s), 7.42 (2H, d, $J=8.4$ Hz), 7.24 (2H, d, $J=8.4$ Hz), 7.06 (1H, s), 6.55 (1H, br.s), 3.03-3.10 (5H, m), 2.72-2.83 (2H, m), 1.33 (3H, t, $J=7.6$ Hz).

STEP 8. 6-chloro-2-ethyl-N-methyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-6-chloro-2-ethyl-N-methyl-1H-benzimidazole-5-carboxamide (step 7).

m.p.: 122-135 °C.

IR (KBr) v: 2877, 1637, 1519, 1400, 1340, 1161, 1091 cm⁻¹

MS (ESI) m/z: 554 (MH⁺), 552 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 7.79-7.84 (3H, m), 7.28-7.33 (4H, m), 7.12 (2H, d, J=8.2 Hz), 6.96 (1H, s), 6.80 (1H, br.s), 6.70 (1H, br.s), 3.48-3.54 (2H, m), 3.08 (3H, d, J=4.8 Hz), 2.89 (2H, t, J=6.9 Hz), 2.72 (2H, q, J=7.5 Hz), 2.41 (3H, s), 1.30 (3H, t, J=7.5 Hz).

EXAMPLE 334

2-(4-{6CHLORO-2-ETHYL-5-[(METHYLAMINO)CARBONYL]-1H-BENZIMIDAZOL-1-YL}PHENYL)ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-(4-{6-chloro-2-ethyl-5-[(methylamino)carbonyl]-1H-benzimidazol-1-yl}phenyl)ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-N-methyl-1H-benzimidazole-5-carboxamide (Example 333, step 4).

m.p.: 201-204 °C.

MS (ESI) m/z: 555 (MH⁺), 553 ([M-H]⁻)

¹H-NMR (DMSO-d₆) δ: 8.27-8.29 (1H, m), 7.76 (2H, d, J=8.1 Hz), 7.69 (1H, s), 7.40-7.48 (6H, m), 7.06 (1H, s), 4.28 (2H, t, J=6.3 Hz), 2.96 (2H, t, J=6.3 Hz), 2.69-2.78 (5H, m), 2.36 (3H, s), 1.23 (3H, t, J=7.5 Hz).

EXAMPLE 335

2-{4-[6CHLORO-5-[(DIMETHYLAMINO)CARBONYL]-2-(1-METHYLETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

5 STEP 1. 2,4-dichloro-*N,N*-dimethyl-5-nitrobenzamide

To a solution of 2,4-dichloro-5-nitrobenzoic acid (4 g, 17 mmol) in toluene (50 ml) was added thionyl chloride (6 ml, 84 mmol) at room temperature. The mixture was stirred at 80 °C for 2 days. The solvent was removed and the residue was dissolved with tetrahydrofuran (30 ml). The mixture was added 50% dimethylamine (760 mg) at 0 °C and the mixture was stirred at room temperature over night. The volatile component was removed under reduced pressure, and the residue was extracted with ethyl acetate (100 ml). The organic layer was washed with water (50 ml), brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (1:1) to afford 3.6 g (82%) of the title compound as pale yellow solids.

¹H-NMR (CDCl₃) δ: 7.90 (1H, s), 7.65 (1H, s), 3.15 (3H, s), 2.91 (3H, s).

STEP 2. 2-chloro-4-{[4-(2-hydroxyethyl)phenyl]amino}-*N,N*-dimethyl-5-nitrobenzamide

20 The title compound was prepared according to the procedure described in step 3 of Example 1 from 2,4-dichloro-*N,N*-dimethyl-5-nitrobenzamide (step 1).

MS (EI) *m/z*: 363 (M⁺)

¹H-NMR (CDCl₃) δ: 9.52 (1H, br.s), 8.20 (1H, s), 7.34 (2H, d, J=8.2 Hz), 7.22 (2H, d, J=8.2 Hz), 7.16 (1H, s), 3.92 (2H, m), 3.13 (3H, s), 2.89-2.94 (5H, m).

STEP 3. 5-amino-2-chloro-4-{[4-(2-hydroxyethyl)phenyl]amino}-*N,N*-dimethylbenzamide

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-chloro-4-{{[4-(2-hydroxyethyl)phenyl]amino}-*N,N*-dimethyl-5-nitrobenzamide (step 2).

¹H-NMR (CDCl₃) δ: 7.05-7.11 (3H, m), 6.79 (2H, d, J=8.5 Hz), 6.63 (1H, s),
5.59 (1H, s), 3.79-3.83 (4H, m), 3.11 (3H, s), 2.92 (3H, s), 2.79 (2H, t, J=6.4 Hz).

STEP 4. 2-{4-[6-chloro-5-[(dimethylamino)carbonyl]-2-(1-methylethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 5-amino-2-chloro-4-{{[4-(2-hydroxyethyl)phenyl]amino}-*N,N*-dimethylbenzamide (step 3).

STEP 5. 6-chloro-1-[4-(2-hydroxyethyl)phenyl]-*N,N*-dimethyl-2-(1-methylethyl)-1*H*-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[6-chloro-5-[(dimethylamino)carbonyl]-2-(1-methylethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl propanoate (step 4).

MS (EI) m/z: 371 (M⁺)

¹H-NMR (CDCl₃) δ: 7.66 (1H, s), 7.46 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.12 (1H, s), 3.95-4.00 (2H, m), 3.17 (3H, s), 3.00 (2H, d, J=6.6 Hz), 2.87 (3H, s), 2.78 (2H, q, J=7.5 Hz), 1.34 (3H, t, J=7.5 Hz).

STEP 6. 2-{4-[6-chloro-5-[(dimethylamino)carbonyl]-2-(1-methylethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 6-chloro-1-[4-(2-hydroxyethyl)phenyl]-*N,N*-dimethyl-2-(1-methylethyl)-1*H*-benzimidazole-5-carboxamide (step 5).

m.p.: 173-176 °C.

IR (KBr) v: 1741, 1637, 1519, 1398, 1344, 1159, 1078, 904 cm⁻¹

MS (ESI) m/z: 569 (MH⁺), 567 ([M-H])

¹H-NMR (CDCl₃) δ: 7.93 (2H, d, J=8.4 Hz), 7.70 (1H, s), 7.27-7.34 (4H, m), 7.09-7.12 (3H, m), 4.35 (2H, t, J=6.6 Hz), 3.19 (3H, s), 2.98 (2H, t, J=6.6 Hz), 2.88 (3H, s), 2.74 (2H, q, J=7.5 Hz), 2.42 (3H, s), 1.29 (3H, t, J=7.5 Hz).

5 EXAMPLE 336

2-(4-{6-CHLORO-2-ETHYL-5-[(METHYLOXY)METHYL]-1H-BENZIMIDAZOL-1-YL}PHENYL)ETHYL (4-METHYLPHENYL)SUKLFONYLCARBAMATE

STEP 1. 1,5-dichloro-2-[(methyloxy)methyl]-4-nitrobenzene

- 10 To a solution of 1,5-dichloro-2-(chloromethyl)-4-nitrobenzene (Hagmann, William K.; Dorn, Conrad P.; Frankshun, Robert A.; O'Grady, Laura A.; Bailey, Philip J.; et al.; JMCMAR; J.Med.Chem.; EN; 29; 8; 1986; 1436-1441, 10.6 g, 44 mmol) in methanol (30 ml) was added sodium methoxide (44 ml, 66 mmol) at room temperature. The mixture was stirred at 80 °C for 21 h.
- 15 The volatile component was removed under reduced pressure, and the residue was extracted with ethyl acetate (100 ml). The organic layer was washed with water (50 ml), brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (6:1/4:1) to afford 2.8 g (27%) of the title compound as pale
- 20 yellow oil.

¹H-NMR (CDCl₃) δ: 8.01 (1H,s), 7.09 (1H, s), 4.49 (2H, s), 3.96 (3H, s).

STEP 2. 2-[4-{5-chloro-4-[(methyloxy)methyl]-2-nitrophenyl}amino)phenyl]ethanol

- The title compound was prepared according to the procedure described
- 25 in step 3 of Example 1 from 1,5-dichloro-2-[(methyloxy)methyl]-4-nitrobenzene (step 1).

¹H-NMR (CDCl₃) δ: 9.45 (1H, br.s), 8.28 (1H, s), 7.17-7.33 (5H, m), 4.44 (2H, s), 3.91 (1H, br.s), 3.45 (3H, s), 2.91 (2H, t, J=6.6 Hz).

STEP 3. 2-[4-({2-amino-5-chloro-4-[(methyloxy)methyl]phenyl}amino)phenyl]ethanol

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-[4-({5-chloro-4-[(methyloxy)methyl]-2-nitrophenyl}amino)phenyl]ethanol (step 2).

¹H-NMR (CDCl₃) δ: 7.07-7.01 (3H, m), 6.88 (1H, s), 6.74 (2H, d, J=8.4 Hz), 5.16 (1H, br.s), 4.47 (2H, s), 3.82 (2H, t, J=6.6 Hz), 3.71 (2H, br.s), 3.46 (3H, s), 2.79 (2H, t, J=6.6 Hz).

STEP 4. 2-(4-{6-chloro-2-ethyl-5-[(methyloxy)methyl]-1H-benzimidazol-1-yl}phenyl)ethanol

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-({2-amino-5-chloro-4-[(methyloxy)methyl]phenyl}amino)phenyl]ethanol (step 3).

MS (EI) m/z: 344 (M⁺)

¹H-NMR (CDCl₃) δ: 7.82 (1H, s), 7.46 (2H, d, J=8.2 Hz), 7.28 (2H, d, J=8.2 Hz), 7.12 (1H, s), 4.65 (1H, s), 3.99 (2H, br.s), 3.45 (3H, s), 3.00 (3H, t, J=7.6 Hz), 2.78 (2H, q, J=7.6 Hz), 1.34 (3H, t, J=7.6 Hz).

STEP 5. 2-(4-{6-chloro-2-ethyl-5-[(methyloxy)methyl]-1H-benzimidazol-1-yl}phenyl)ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-(4-{6-chloro-2-ethyl-5-[(methyloxy)methyl]-1H-benzimidazol-1-yl}phenyl)ethanol (step 4).

m.p.: 174.5 °C.

IR (KBr) ν: 3377, 2813, 1718, 1519, 1398, 1342, 1159, 1093, 1062 cm⁻¹

MS (ESI) m/z: 542 (MH⁺), 540 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 7.94 (2H, d, J=8.2 Hz), 7.83 (1H, s), 7.08-7.33 (7H, m), 4.64 (s, 2H), 4.37 (2H, t, J=6.4 Hz), 3.46 (3H, s), 2.97 (2H, t, J=6.4 Hz), 2.73 (2H, q, J=7.5 Hz), 2.42 (3H, s), 1.26 (3H, t, J=7.5 Hz).

EXAMPLE 337

5 2-{4-[6-CHLORO-2-ETHYL-5-(HYDROXYMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[6-chloro-5-(chloromethyl)-2-ethyl-1H-benzimidazol-1-yl]phenyl}ethanol

10 The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-[4-({2-amino-5-chloro-4-[(methyloxy)methyl]phenyl}amino)phenyl]ethanol (Example 336, step 3).

MS (EI) m/z: 348 (M⁺)

15 ¹H-NMR (CDCl₃) δ: 7.83 (1H, s), 7.46 (2H, d, J=8.2 Hz), 7.27 (2H, d, J=8.2 Hz), 7.15 (1H, s), 4.84 (2H, s), 3.96-4.02 (2H, m), 3.00 (2H, t, J=6.4 Hz), 2.77 (2H, q, J=7.5 Hz), 1.34 (2H, t, J=7.5 Hz).

STEP 2. 6-chloro-5-(chloromethyl)-1-[4-(2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}ethyl)phenyl]-2-ethyl-1H-benzimidazole

20 The title compound was prepared according to the procedure described in step 2 of Example 90 from 2-{4-[6-chloro-5-(chloromethyl)-2-ethyl-1H-benzimidazol-1-yl]phenyl}ethanol

(step 1).

MS (EI) m/z: 405 (M⁺)

25 ¹H-NMR (CDCl₃) δ: 7.83 (1H, s), 7.43 (2H, d, J=8.4 Hz), 7.23 (2H, d, J=8.4 Hz), 7.11 (1H, s), 4.85 (2H, s), 3.91 (2H, t, J=6.4 Hz), 2.94 (2H, t, J=6.4 Hz), 2.76 (2H, q, J=7.5 Hz), 1.33 (3H, t, J=7.5 Hz), 0.87 (9H, s), 0.00 (6H, s).

STEP 3. {6-chloro-1-[4-(2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}ethyl)phenyl]-2-

00977761.101501

ethyl-1*H*-benzimidazol-5-yl)methyl propanoate

To a solution of 6-chloro-5-(chloromethyl)-1-[4-(2- $\{[(1,1$ -dimethylethyl)(dimethyl)silyl]oxy}ethyl)phenyl]-2-ethyl-1*H*-benzimidazole (step 2, 403 mg, 0.86 mmol) in N, N-dimethylformamide (10 ml) was added propionic acid (0.06 ml, 0.86 mmol) and NaHCO₃ (144 mg, 1.72 mmol) at room temperature. The mixture was stirred at 60 °C for 7 h. The mixture was added water (50 ml) and extracted with ethyl acetate(100 ml). The organic layer was washed with brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (8:1/4:1) to afford 235 mg (53%) of the title compound as pale yellow oil.

¹H-NMR (CDCl₃) δ : 7.81 (1H, s), 7.43 (2H, d, J=8.5 Hz), 7.24 (2H, d, J=8.5 Hz), 7.11 (1H, s), 5.33 (2H, s), 3.91 (2H, t, J=6.6 Hz), 2.93 (2H, t, J=6.6 Hz), 2.77 (2H, q, J=7.5 Hz), 2.42 (2H, q, J=7.5 Hz), 1.33 (3H, t, J=7.5 Hz), 1.18 (3H, t, J=7.5 Hz), 0.87 (9H, s), 0.00 (6H, s).

STEP 4. {6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazol-5-yl)methyl propanoate

The title compound was prepared according to the procedure described in step 6 of Example 90 from {6-chloro-1-[4-(2- $\{[(1,1$ -dimethylethyl)(dimethyl)silyl]oxy}ethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl)methyl propanoate (step 3).

MS (EI) m/z: 386 (M⁺)

¹H-NMR (CDCl₃) δ : 7.70 (1H, s), 7.37 (2H, d, J=8.3 Hz), 7.17 (2H, d, J=8.3 Hz), 7.04 (1H, s), 5.21 (2H, s), 3.88 (2H, d, J=6.6 Hz), 2.91 (2H, t, J=6.6 Hz), 2.67 (2H, q, J=7.5 Hz), 2.32 (2H, q, J=7.5 Hz), 1.24 (3H, t, J=7.5 Hz), 1.08 (3H, t, J=7.5 Hz).

STEP 5. [6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyloxy)ethyl}phenyl)-1*H*-benzimidazol-5-yl)methyl propanoate

The title compound was prepared according to the procedure described in Example 3 from {6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazol-5-yl} methyl propanoate (step 4).

¹H-NMR (CDCl₃) δ: 7.92 (2H, d, J=8.3 Hz), 7.81 (1H, s), 7.32-7.36 (4H, m), 7.21-7.25 (2H, m), 7.10 (1H, s), 5.32 (2H, s), 4.38 (2H, t, J=6.7 Hz), 3.02 (2H, t, J=6.7 Hz), 2.76 (2H, q, J=7.6 Hz), 2.37-2.49 (5H, m), 1.33 (3H, t, J=7.6 Hz), 1.18 (3H, t, J=7.6 Hz).

STEP 6. 2-{4-[6-chloro-2-ethyl-5-(hydroxymethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonyl carbamate

The title compound was prepared according to the procedure described in step 6 of Example 1 from [6-chloro-2-ethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyloxy)ethyl}phenyl)-1*H*-benzimidazol-5-yl)methyl propanoate (step 5).

m.p.: 172.7 °C.

IR (KBr) v: 1745, 1519, 1240, 1160, 1089, 1058 cm⁻¹

MS (ESI) m/z: 528 (MH⁺), 526 ([M-H])

¹H-NMR (DMSO-d₆) δ: 7.74-7.77 (3H, m), 7.39-7.46 (6H, m), 7.03 (1H, s), 4.63 (2H, s), 4.27 (2H, t, J=6.6 Hz), 2.95 (2H, t, J=6.6 Hz), 2.72 (2H, q, J=7.5 Hz), 2.34 (3H, s), 1.23 (3H, t, J=7.5 Hz).

EXAMPLE 338

N-[{2-(4-{6-CHLORO-2-ETHYL-5-[(METHYLOXY)METHYL]-1*H*-BENZIMIDAZOL-1-YL}PHENYL)ETHYL}AMINO}CARBONYL]-4-METHYLBENZENSULFONAMIDE

STEP 1. 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-5-[(methyloxy)methyl]-1H-benzimidazole

The title compound was prepared according to the procedure described in step 5 of Example 26 from 2-(4-{6-chloro-2-ethyl-5-[(methyloxy)methyl]-1H-

5 benzimidazol-1-yl}phenyl)ethanol (Example 336, step 4).

MS (EI) m/z: 369 (M⁺)

¹H-NMR (CDCl₃) δ: 7.82 (1H, s), 7.45 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 7.11 (1H, s), 4.65 (2H, s), 3.62 (2H, t, J=7.0 Hz), 3.45 (3H, s), 3.02 (2H, t, J=7.0 Hz), 2.77 (2H, q, J=7.7 Hz), 1.34 (3H, t, J=7.7 Hz).

10 STEP 2. 2-(4-{6-chloro-2-ethyl-5-[(methyloxy)methyl]-1H-benzimidazol-1-yl}phenyl)ethanamine

The title compound was prepared according to the procedure described in step 9 of Example 1 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-ethyl-5-[(methyloxy)methyl]-1H-benzimidazole (step 1).

15 ¹H-NMR (CDCl₃) δ: 7.82 (1H, s), 7.42 (2H, d, J=8.4 Hz), 7.24-7.29 (2H, m), 7.12 (1H, s), 4.65 (1H, s), 3.45 (3H, ds), 3.08 (2H, t, J=6.7 Hz), 2.88 (2H, t, J=6.7 Hz), 2.77 (2H, q, J=7.6 Hz), 1.34 (3H, t, J=7.6 Hz).

STEP 3. N-([2-(4-{6-chloro-2-ethyl-5-[(methyloxy)methyl]-1H-benzimidazol-1-yl}phenyl)ethyl]amino)carbonyl)-4-methylbenzenesulfonamide

20 The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-(4-{6-chloro-2-ethyl-5-[(methyloxy)methyl]-1H-benzimidazol-1-yl}phenyl)ethanamine (step 2).

m.p.: 134.6 °C.

IR (KBr) v: 3377, 2813, 1718, 1519, 1398, 1342, 1159, 1093, 1062 cm⁻¹

25 MS (ESI) m/z: 541 (MH⁺), 539 ([M-H]⁻)

0397761.10501

¹H-NMR (CDCl₃) δ: 7.82 (1H, s), 7.72 (2H, d, J=8.4 Hz), 7.24-7.39 (4H, m), 7.09 (1H, s), 6.72 (1H, br.s), 4.65 (2H, s), 3.57 (2H, m), 3.45 (3H, s), 2.93 (2H, d, J=6.8 Hz), 2.77 (2H, q, J=7.5 Hz), 2.40 (3H, s), 1.32 (3H, t, J=7.5 Hz).

EXAMPLE 339

2-{4-[6-CHLORO-2-[3-(4PYRIDINYL)PROPYL]-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate

To a mixture of 2-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)ethanol (Example 104, step 1, 8.1 g, 22.4 mmol) and pyridine (1.8 ml, 22.45 mmol) in dichloromethane (200 ml) was added acetyl chloride (1.6 ml, 22.4 mmol) at 0 °C. The mixture was stirred at 0 °C for 45 min. The mixture was added water (50 ml) and extracted with dichloromethane (300 ml). The organic layer was washed with brine (100 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (2:1) to afford 8.6 g (95%) of the title compound as yellow solids.

¹H-NMR (CDCl₃) δ: 9.68 (1H, br.s), 8.57 (1H, s), 7.35 (2H, d, J=8.4 Hz), 7.22 (2H, d, J=8.4 Hz), 7.17 (1H, s), 4.33 (2H, t, J=7.0 Hz), 3.00 (2H, t, J=7.0 Hz), 2.06 (3H, s).

STEP 2. 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate

The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-(4-{[5-chloro-2-nitro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (step 1).

¹H-NMR (CDCl₃) δ: 7.13-7.16 (3H, m), 7.06 (1H, s), 6.89 (2H, d, J=8.4 Hz), 5.43 (1H, br.s), 4.26 (2H, t, J=7.2 Hz), 3.69 (2H, br.s), 2.89 (2H, d, J=7.2 Hz), 2.04 (3H, s).

STEP 3. 2-(4-([5-chloro-2-{4-(4-pyridinyl)butanoyl}amino}-4-

5 (trifluoromethyl)phenyl]amino}phenyl)ethyl acetate

A mixture of 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (step 2, 250 mg, 0.67 mmol), 4-(4-pyridinyl)butanoic acid (200 mg, 1 mmol), and WSC (191 mg, 1 mmol) in dichloromethane (7 ml) was stirred at room temperature for 1.5 h. The mixture was added water (5 ml) and extracted with dichloromethane (30 ml). The organic layer was washed with brine (5 ml), then dried (Na₂SO₄). The solvent was removed under reduced pressure to afford the title compound as pale brown amorphous.

MS (EI) m/z: 519 (M⁺)

15 STEP 4. 2-{4-[6-chloro-2-[3-(4-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol

A mixture of 2-(4-{[5-chloro-2-{4-(4-pyridinyl)butanoyl}amino}-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (step 3, 220 mg, 0.42 mmol) and 2N NaOH (15 ml) in ethanol (20 ml) was stirred at 40 °C for 7 h. The solvent was removed and the residue was added water (50 ml). The mixture was extracted with ethyl acetate (100 ml). The organic layer was washed with brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with dichloromethane:methanol (20:1) to afford 105 mg (54%) of the title compound as pale brown oil.

¹H-NMR (CDCl₃) δ: 8.40-8.42 (2H, m), 8.10 (1H, s), 7.43 (2H, d, J=8.3 Hz), 7.16-7.19 (3H, m), 7.02 (2H, d, J=6.0 Hz), 4.00 (2H, t, J=6.2 Hz), 3.00 (2H, t, J=6.2 Hz), 2.75 (2H, t, J=7.3 Hz), 2.68 (2H, t, J=7.3 Hz), 2.11-2.19 (2H, m).

STEP 5. 2-{4-[6-chloro-2-[3-(4-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[6-chloro-2-[3-(4-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol (step 4).

m.p.: 80-87 °C.

IR (KBr) ν: 1743, 1610, 1517, 1431, 1346, 1161 cm⁻¹

MS (ESI) m/z: 657 (MH⁺), 655 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 8.32 (2H, d, J=6.0 Hz), 8.09 (1H, s), 7.99 (2H, d, J=8.2 Hz), 7.34 (2H, d, J=8.2 Hz), 7.22 (2H, d, J=8.2 Hz), 7.15 (1H, s), 6.94-7.02 (4H, m), 4.48 (2H, t, J=5.4 Hz), 3.01 (2H, t, J=5.4 Hz), 2.74 (2H, t, J=6.0 Hz), 2.54 (2H, t, J=7.9 Hz), 2.44 (3H, s), 2.16-2.21 (2H, m).

EXAMPLE 340

2-{4-[6-CHLORO-2-[3-(3-PYRIDINYL)PROPYL]-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-(4-{[5-chloro-2-{[4-(3-pyridinyl)butanoyl]amino}-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate

The title compound was prepared according to the procedure described in step 3 of Example 339 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2).

¹H-NMR (CDCl₃) δ: 8.43 (2H, br.s), 7.50-7.71 (2H, m), 7.15-7.28 (6H, m), 6.96 (2H, d, J=8.3 Hz), 6.43 (1H, br.s), 4.26 (2H, t, J=7.0 Hz), 2.90 (2H, t, J=7.0 Hz), 2.70 (2H, t, J=7.3 Hz), 2.41 (2H, t, J=7.3 Hz), 2.03-2.08 (5H, m).

STEP 2. 2-{4-[6-chloro-2-[3-(3-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in step 4 of Example 339 from 2-(4-{[5-chloro-2-{[4-(3-

- 5 pyridinyl)butanoyl]amino}-4-(trifluoromethyl)phenyl]amino)phenyl)ethyl acetate (step 1).

MS (EI) m/z: 459 (M⁺)

- ¹H-NMR (CDCl₃) δ: 8.33 (1H, d, J=4.4 Hz), 8.09 (1H, s), 7.62 (1H, s), 7.43-7.50 (3H, m), 7.16-7.22 (4H, m), 4.02 (2H, t, J=5.6 Hz), 2.99 (2H, t, J=5.6 Hz),
10 2.74 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=6.6 Hz), 2.04-2.13 (2H, m).

STEP 3. 2-{4-[6-chloro-2-[3-(3-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[6-chloro-2-[3-(3-pyridinyl)propyl]-5-(trifluoromethyl)-

- 15 1H-benzimidazol-1-yl]phenyl}ethanol (step 2).

m.p.: 90-95 °C.

IR (KBr) v: 1743, 1517, 1431, 1346, 1301, 1161, 1130, 1085 cm⁻¹

MS (ESI) m/z: 657 (MH⁺), 655 ([M-H]⁻)

- ¹H-NMR (CDCl₃) δ: 8.59 (1H, dd, J=1.7 Hz, 5.1 Hz), 8.08 (1H, s), 7.95 (2H, d, J=8.3 Hz), 7.86 (1H, d, J=1.7 Hz), 7.54-7.58 (1H, m), 7.27-7.34 (5H, m), 7.20 (1H, s), 7.12 (2H, d, J=8.4 Hz), 4.46 (2H, t, J=5.1 Hz), 3.00 (2H, t, J=5.1 Hz), 2.77-2.82 (2H, m), 2.62 (2H, t, J=7.0 Hz), 2.43 (3H, s), 1.85-1.91 (2H, m).

EXAMPLE 341

- 20 2-{4-[6-CHLORO-2-[3-OXO-3-(3-PYRIDINYL)PROPYL]-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-(4-{[5-chloro-2-{[4-oxo-4-(3-pyridinyl)butanoyl]amino}-4-

(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate

The title compound was prepared according to the procedure described in step 3 of Example 339 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2).

- 5 ¹H-NMR (CDCl₃) δ: 9.19 (1H, d J=2.2 Hz), 8.80 (1H, dd J=1.8 Hz 3.9 Hz), 8.20 (1H, d J=7.9 Hz), 7.64 (2H, br.s), 7.44 (1H, dd, J=5.8 Hz, 7.9 Hz), 7.28 (1H, s), 7.19 (2H, d, J=8.3 Hz), 7.05 (2H, d, J=8.3 Hz), 6.70 (1H, br.s), 4.27 (2H, t, J=7.1 Hz), 3.49 (2H, t, J=5.5 Hz), 2.92 (2H, t, J=7.1 Hz), 2.78 (2H, t, J=5.8 Hz), 2.05 (3H, s).

- 10 STEP 2. 3-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-yl]-1-(3-pyridinyl)-1-propanone

The title compound was prepared according to the procedure described in step 4 of Example 339 from 2-(4-{[5-chloro-2-{[4-oxo-4-(3-pyridinyl)butanoyl]amino}-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (step 1).

- 15 ¹H-NMR (CDCl₃) δ: 9.05-9.06 (1H, m), 8.77-8.79 (1H, m), 8.24-8.28 (1H, m), 8.06 (1H, s), 7.54 (2H, d, J=8.5 Hz), 7.40-7.46 (3H, m), 3.97-4.04 (2H, m), 3.66 (2H, t, J=7.0 Hz), 3.19 (2H, t, J=7.0 Hz), 3.02 (2H, t, J=6.4 Hz).

- 20 STEP 3. 2-{4-[6-chloro-2-[3-oxo-3-(3-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 3-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-yl]-1-(3-pyridinyl)-1-propanone (step 2). m.p.: 89-95 °C.

- 25 IR (KBr) v: 2972, 1747, 1693, 1517, 1346, 1230, 1161, 1085 cm⁻¹
MS (ESI) m/z: 671 (MH⁺), 669 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 8.91 (1H, s), 8.83-8.85 (1H, m), 8.23-8.27 (1H, m), 8.05 (1H, s), 7.92 (2H, d, J=8.2 Hz), 7.33-7.48 (7H, m), 7.21 (1H, s), 4.43 (2H, t, J=6.3 Hz), 3.47 (2H, t, J=7.1 Hz), 3.25 (2H, t, J=7.1 Hz), 3.04 (2H, t, J=6.3 Hz), 2.43 (3H, s).

5 EXAMPLE 342

2-[4-[6-CHLORO-2-[3-OXO-3-(2-PYRIDINYL)PROPYL]-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL]ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-(4-{[5-chloro-2-{[4-oxo-4-(2-pyridinyl)butanoyl]amino}-4-

10 (trifluoromethyl)phenyl]amino}phenyl)ethyl acetate

The title compound was prepared according to the procedure described in step 3 of Example 339 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2). MS (EI) m/z: 533 (M⁺)

15 STEP 2. 2-[4-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-yl]-1-(2-pyridinyl)-1-propanone

The title compound was prepared according to the procedure described in step 4 of Example 339 from 2-(4-{[5-chloro-2-{[4-oxo-4-(2-pyridinyl)butanoyl]amino}-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (step 1).

¹H-NMR (CDCl₃) δ: 8.67-8.69 (1H, m), 7.84 (1H, s), 7.96-7.99 (1H, m), 7.81-7.84 (1H, m), 7.39-7.51 (5H, m), 7.23 (1H, s), 3.96-4.02 (2H, m), 3.91 (2H, t, J=6.9 Hz), 3.15 (2H, t, J=6.9 Hz), 3.01 (2H, t, J=6.4 Hz).

STEP 3. 2-[4-[6-chloro-2-[3-oxo-3-(2-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate

25 benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in of Example 3 from 3-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-yl]-1-(2-pyridinyl)-1-propanone (step 2).
m.p.: 233.6 °C.

- 5 IR (KBr) v: 1743, 1703, 1515, 1481, 1336, 1203, 1120, 1087, 995 cm^{-1}
MS (ESI) m/z: 671 (MH^+), 669 ($[\text{M}-\text{H}]^-$)
 ^1H -NMR ($\text{DMSO}-d_6$) δ : 8.74-8.76 (1H, m), 8.13 (1H, s), 7.90-8.03 (2H, m), 7.77 (2H, d, $J=8.1$ Hz), 7.66-7.70 (1H, m), 7.49-7.58 (4H, m), 7.42 (2H, d, $J=8.1$ Hz), 7.34 (1H, s), 4.30 (2H, t, $J=6.4$ Hz), 3.83 (2H, t, $J=6.4$ Hz), 3.09 (2H, t, $J=6.4$ Hz), 2.98 (2H, t, $J=6.4$ Hz), 2.50 (3H, s).

EXAMPLE 343

2-[4-[6-CHLORO-2-[3-(2PYRIDINYL)PROPYL]-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

- 15 STEP 1. 2-(4-{[5-chloro-2-{[4-(2-pyridinyl)butanoyl]amino}-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate

The title compound was prepared according to the procedure described in step 3 of Example 339 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2).

- 20 ^1H -NMR (CDCl_3) δ : 9.26 (1H, br.s), 8.39-8.41 (1H, m), 7.86 (1H, s), 7.69-7.72 (1H, m), 7.49 (1H, s), 7.25-7.28 (1H, m), 7.15-7.21 (3H, m), 7.00 (2H, d, $J=8.4$ Hz), 4.27 (2H, t, $J=7.1$ Hz), 2.98 (2H, t, $J=6.3$ Hz), 2.91 (2H, t, $J=7.1$ Hz), 2.33 (2H, t, $J=5.9$ Hz), 2.05 (3H, s).

STEP 2. 2-[4-[6-chloro-2-[3-(2-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethanol

- 25 The title compound was prepared according to the procedure described in step 4 of Example 339 from 2-(4-{[5-chloro-2-{[4-(2-

pyridinyl)butanoyl]amino}-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (step 1).

¹H-NMR (CDCl₃) δ: 8.43-8.45 (1H, m), 8.09 (1H, s), 7.53-7.59 (1H, m), 7.45 (2H, d, J=8.2 Hz), 7.22-7.25 (3H, m), 7.05-7.13 (2H, m), 3.98 (2H, t, J=6.3 Hz), 3.00 (2H, t, J=6.3 Hz), 2.84 (4H, t, J=7.5 Hz), 2.18-2.22 (2H, m), 1.81-1.90 (2H, m).

STEP 3. 2-{4-[6-chloro-2-[3-(2-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[6-chloro-2-[3-(2-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethanol (step 2).

m.p.: 193 °C.

IR (KBr) v: 1747, 1626, 1517, 1433, 1350, 1159, 1120, 1085 cm⁻¹

MS (ESI) m/z: 657 (MH⁺), 655 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 8.47-8.49 (1H, m), 8.08 (1H, s), 7.90 (2H, d, J=8.4 Hz), 7.60-7.66 (1H, m), 7.36 (2H, d, J=8.4 Hz), 7.11-7.22 (7H, m), 4.44 (2H, t, J=6.0 Hz), 3.01 (2H, t, J=6.0 Hz), 2.82-2.88 (4H, m), 2.45 (3H, s), 1.84-1.94 (2H, m).

EXAMPLE 344

2-{4-[6-CHLORO-2-[3-(2-PYRIDINYL)PROPYL]-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE P-TOLUENESULFONATE

The title compound was prepared according to the procedure described in Example 231 from 2-{4-[6-chloro-2-[3-(2-pyridinyl)propyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

(Example 343)

m.p.: 108-110 °C.

IR (KBr) v: 3062, 1745, 1456, 1232, 1163, 1010 cm⁻¹

EXAMPLE 345

N-{[(2-{4-[2-ethyl-5-(1-hydroxyethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

- 5 STEP 1. *N*-{[(2-{4-[2-ethyl-5-(1-hydroxyethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

A mixture *N*-{[(2-{4-(5-acetyl-2-ethyl-1*H*-benzimidazol-1-yl)phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (Example 78, 238 mg, 0.47 mmol) and 2*N* NaOH (0.1 ml) in ethanol (10 ml) was added a
10 mixture of NaBH₄ (178 mg, 0.47 mmol) and 2*N* NaOH (0.1 ml) in ethanol (4 ml) at room temperature. The mixture was stirred at room temperature for 4 h. The mixture was added water (10 ml) and neutralized with NH₄Cl. The mixture was extracted with ethyl acetate (50 ml). The organic layer was washed with
15 brine (10 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (1:4/1:6) /CH₂Cl₂:methanol(10:1) to afford 198 mg (83%) of the title compound as white solids.
m.p.: 190 °C.

IR (KBr) ν : 3384, 2979, 1716, 1514, 1404, 1159, 1087 cm⁻¹

- 20 MS (ESI) m/z : 507 (MH⁺), 505 ([M-H]⁻)

¹H-NMR (CDCl₃) δ : 7.73-7.76 (3H, m), 7.21-7.34 (7H, m), 7.20 (1H, d, J=8.5 Hz), 6.66 (1H, br.s), 5.02 (1H, q, J=6.4 Hz), 3.52-3.59 (2H, m), 2.91 (2H, t, J=7.0 Hz), 2.75 (2H, q, J=7.5 Hz), 2.39 (3H, s), 1.54 (3H, d, J=6.4 Hz), 1.30 (3H, t, J=7.5 Hz).

- 25 EXAMPLE 346

N-{[(2-{4-[2-ETHYL-5-(1-HYDROXYETHYL)-1*H*-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-
METHYLBENZENESULFONAMIDE *P*-TOLUENESULFONATE

The title compound was prepared according to the procedure described
5 in Example 231 from *N*-{[(2-{4-[2-ethyl-5-(1-hydroxyethyl)-1*H*-benzimidazol-
1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (Example
345)

m.p.: 110-115 °C.

IR (KBr) ν : 3062, 1708, 1519, 1340, 1163 cm^{-1}

10 EXAMPLE 347

N-{[(2-{4-[2-ETHYL-5-[1-(METHYLOXY)ETHYL]-1*H*-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-
METHYLBENZENESULFONAMIDE

STEP 1. *N*-{[(2-{4-[2-ethyl-5-[1-(methyloxy)ethyl]-1*H*-benzimidazol-1-
15 yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

A solution of *N*-{[(2-{4-[2-ethyl-5-(1-hydroxyethyl)-1*H*-benzimidazol-
1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (Example
345, 151 mg, 0.3 mmol) in CH_2Cl_2 (15 ml) was added thionyl chloride (0.1 ml,
1.5 mmol) at room temperature. The mixture was stirred at room temperature
20 for 2 h. The solvent was removed and the residue was dissolved with methanol
(15 ml). The mixture was added triethylamine (0.08 ml, 0.6 mmol) and stirred at
room temperature for 5 h. The solvent was removed and the residue was
extracted with CH_2Cl_2 (50 ml). The organic layer was washed with water (10
ml), brine (10 ml), then dried (Na_2SO_4). After removal of solvent, the crude
25 product was purified by flash column chromatography eluting with hexane/ethyl
acetate (1:6) / CH_2Cl_2 :methanol(10:1) to afford 139 mg (89%) of the title
compound as white solids.

MS (ESI) m/z : 521 (MH^+), 519 ($[M-H]^-$)

1H -NMR ($CDCl_3$) δ : 7.65-7.75 (3H, m), 7.27-7.37 (6H, m), 7.16-7.20 (1H, m), 7.07 (1H, d, $J=8.3$ Hz), 6.69 (1H, br.s), 4.42 (1H, q, $J=6.5$ Hz), 3.54-3.62 (2H, m), 3.22 (3H, s), 2.93 (2H, t, $J=7.0$ Hz), 2.93 (2H, t, $J=7.0$ Hz), 2.78 (2H, q, $J=7.6$ Hz), 2.39 (3H, s), 1.49 (3H, d, $J=6.5$ Hz), 1.32 (3H, t, $J=7.6$ Hz).

EXAMPLE 348

N-({[2-(4-{2-ETHYL-5-[1-(METHYLOXY)ETHYL]-1H-BENZIMIDAZOL-1-YL}PHENYL)ETHYL]AMINO}CARBONYL)-4-METHYLBENZENESULFONAMIDE P-TOLUENESULFONATE

The title compound was prepared according to the procedure described in Example 231 from *N-({[2-(4-{2-ethyl-5-[1-(methyloxy)ethyl]-1H-benzimidazol-1-yl}phenyl)ethyl]amino}carbonyl)-4-methylbenzenesulfonamide* (Example 347)

m.p.: 110-115 °C.

IR (KBr) ν : 3064, 1710, 1519, 1452, 1340, 1163, 1033 cm^{-1}

EXAMPLE 349

N-({[2-(4-[2-ETHYL-5-(1-HYDROXY-1-METHYLETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL)ETHYL]AMINO}CARBONYL)-4-METHYLBENZENESULFONAMIDE P-TOLUENESULFONATE

STEP 1. *N-({[2-(4-[2-ethyl-5-(1-hydroxy-1-methylethyl)-1H-benzimidazol-1-yl]phenyl)ethyl]amino}carbonyl)-4-methylbenzenesulfonamide*

A solution of *N-({[2-(4-(5-acetyl-2-ethyl-1H-benzimidazol-1-yl)phenyl)ethyl]amino}carbonyl)-4-methylbenzenesulfonamide* (Example 78, 100 mg, 0.19 mmol) in tetrahydrofuran (15 ml) was added MeMgI (1.2 ml, 0.99 mmol) dropwise under nitrogen at 0 °C. The mixture was stirred at 0 °C for 1 h and then was stirred at rt for 30 min. The mixture was added water (10 ml) and extracted with CH_2Cl_2 (50 ml). The organic layer was washed with brine (10

ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with CH₂Cl₂:methanol (30:1/20:1/10:1) to afford 100 mg (97%) of the title compound as white solids. MS (ESI) m/z: 521 (MH⁺), 519 ([M-H]⁻)

- 5 ¹H-NMR (CDCl₃) δ: 7.87 (1H, s), 7.76 (2H, d, J=7.9 Hz), 7.17-7.38 (7H, m), 7.00 (1H, d, J=8.5 Hz), 6.69 (1H, br.s), 3.52 (2H, br.s), 2.88 (2H, br.s), 2.73 (2H, br.s), 2.36 (3H, s), 1.62 (6H, s), 1.27 (3H, m).

STEP 2. *N*-{[(2-{4-[2-ethyl-5-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide *p*-toluenesulfonate

- 10 The title compound was prepared according to the procedure described in Example 231 from *N*-{[(2-{4-[2-ethyl-5-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (Step 1).
m.p.: 146-150 °C.

- 15 IR (KBr) v: 2871, 1685, 1519, 1448, 1340, 1124 cm⁻¹

EXAMPLE 350

2-ETHYL-4,6-DIMETHYL-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE-5-CARBOXAMIDE

- 20 STEP 1. 1-[4-(2-chloroethyl)phenyl]-2-ethyl-4,6-dimethyl-1*H*-benzimidazole-5-carboxamide

- 25 A solution of 1-[4-(2-chloroethyl)phenyl]-2-ethyl-4,6-dimethyl-1*H*-benzimidazole-5-carbonitrile (Example 329, step 6, 997 mg, 2.95 mmol) in c.H₂SO₄ (50 ml) was stirred at 80 °C for 15 h. The mixture was poured onto ice and was neutralized with NaOH. The mixture was extracted with ethyl acetate (600 ml). The organic layer was washed with brine (300 ml), then dried

(Na₂SO₄). The solvent was removed to afford 871 mg (83%) of the title compound as white solids.

MS (EI) m/z: 355 (M⁺)

¹H-NMR (CDCl₃) δ: 7.43 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 6.73 (1H, s), 6.56 (1H, br.s), 5.88 (1H, br.s), 3.82 (2H, t, J=7.0 Hz), 3.19 (2H, t, J=7.0 Hz), 2.82 (2H, q, J=7.6 Hz), 2.72 (3H, s), 2.41 (3H, s), 1.26 (3H, t, J=7.6 Hz).

STEP 2. 1-[4-(2-azidoethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 8 Example 1 from 1-[4-(2-chloroethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carboxamide (step 1).

¹H-NMR (CDCl₃) δ: 7.44 (2H, d, J=8.4 Hz), 7.27-7.30 (2H, m), 6.73 (1H, s), 5.97 (1H, br.s), 5.72 (1H, br.s), 3.62 (2H, t, J=7.1 Hz), 3.02 (2H, t, J=7.1 Hz), 2.80 (2H, q, J=7.5 Hz), 2.73 (3H, s), 2.42 (3H, s), 1.26 (3H, t, J=7.5 Hz).

STEP 3. 1-[4-(2-aminoethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 9 of Example 1 from 1-[4-(2-azidoethyl)phenyl]-2-ethyl-4,6-dimethyl-1H-benzimidazole-5-carboxamide (step 2).

¹H-NMR (CDCl₃) δ: 7.41 (2H, d, J=8.2 Hz), 7.26 (2H, d, J=8.2 Hz), 6.74 (1H, s), 6.00 (1H, br.s), 5.76 (1H, br.s), 3.07 (2H, t, J=7.1 Hz), 2.87 (2H, t, J=7.1 Hz), 2.81 (2H, q, J=7.5 Hz), 2.74 (3H, s), 2.43 (3H, s), 1.26 (3H, t, J=7.5 Hz).

STEP 4. 2-ethyl-4,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole-5-carboxamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-[4-(2-aminoethyl)phenyl]-2-ethyl-4,6-dimethyl-1*H*-benzimidazole-5-carboxamide (step 3).

MS (ESI) *m/z*: 534 (MH⁺), 532 ([M-H]⁻)

- 5 ¹H-NMR (CD₃OD) δ: 7.88 (1H, s), 7.80 (2H, d, *J*=8.3 Hz), 7.25-7.42 (6H, m), 6.74 (1H, br.s), 3.42 (2H, t, *J*=6.8 Hz), 2.86 (2H, t, *J*=6.8 Hz), 2.79 (2H, q, *J*=7.6 Hz), 2.65 (3H, s), 2.37 (3H, s), 2.34 (3H, s), 1.21 (3H, t, *J*=7.6 Hz).

- STEP 5. 2-ethyl-4,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide *p*-toluenesulfonate
- 10

The title compound was prepared according to the procedure described in Example 231 from 2-ethyl-4,6-dimethyl-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino}ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide (step 4).

- 15 EXAMPLE 351

N-{[(2-{4-[2-ETHYL-5-(TRIFLUOROACETYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE *P*-TOLUENESULFONATE

- STEP 1. 2,2,2-trifluoro-1-(4-{[4-(2-hydroxyethyl)phenyl]amino}-3-nitrophenyl)ethanone
- 20

The title compound was prepared according to the procedure described in step 1 of Example 45 from 1-(4-amino-3-nitrophenyl)-2,2,2-trifluoroethanone.

¹H-NMR (CDCl₃) δ: 9.47 (1H, br.s), 8.10 (1H, d, *J*=2.6 Hz), 7.16-7.33 (6H, m), 3.87-3.94 (2H, m), 2.91 (2H, t, *J*=6.4 Hz), 1.43 (1H, t, *J*=5.6 Hz).

- 25 STEP 2. 1-(3-amino-4-{[4-(2-hydroxyethyl)phenyl]amino}phenyl)-2,2,2-trifluoroethanone

The title compound was prepared according to the procedure described in step 4 of Example 1 from 2,2,2-trifluoro-1-(4-{[4-(2-hydroxyethyl)phenyl]amino}-3-nitrophenyl)ethanone (step 1).

¹H-NMR (CDCl₃) δ: 7.05-7.09 (3H, m), 6.57-6.70 (4H, m), 3.82 (2H, t, J=6.6 Hz), 2.78 (2H, t, J=6.6 Hz).

STEP 3. 2-[4-[2-ethyl-5-(trifluoroacetyl)-1H-benzimidazol-1-yl]phenyl]ethyl propanoate

The title compound was prepared according to the procedure described in step 5 of Example 1 from 1-(3-amino-4-{[4-(2-hydroxyethyl)phenyl]amino}phenyl)-2,2,2-trifluoroethanone (step 2).

¹H-NMR (CDCl₃) δ: 7.65 (1H, s), 7.45 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 7.06 (2H, s), 4.38 (2H, t, J=6.9 Hz), 3.07 (2H, t, J=6.9 Hz), 2.79 (2H, q, J=7.4 Hz), 2.35 (2H, q, J=7.5 Hz), 1.35 (3H, t, J=7.4 Hz), 1.14 (3H, t, J=7.5 Hz).

STEP 4. 1-{2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazol-5-yl}-2,2,2-trifluoroethanone

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[2-ethyl-5-(trifluoroacetyl)-1H-benzimidazol-1-yl]phenyl}ethyl propanoate (step 3).

¹H-NMR (CDCl₃) δ: 7.65 (1H, s), 7.47 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.06 (2H, s), 3.96-4.03 (2H, m), 3.01 (2H, t, J=6.6 Hz), 2.79 (2H, q, J=7.6 Hz), 1.35 (3H, t, J=7.6 Hz).

STEP 5. 1-{1-[4-(2-chloroethyl)phenyl]-2-ethyl-1H-benzimidazol-5-yl}-2,2,2-trifluoroethanone

The title compound was prepared according to the procedure described in step 7 Example 1 from 1-{2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1H-benzimidazol-5-yl}-2,2,2-trifluoroethanone (step 4).

¹H-NMR (CDCl₃) δ: 7.66 (1H, s), 7.45 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 7.07 (2H, s), 3.82 (2H, t, J=7.0 Hz), 3.20 (2H, t, J=7.0 Hz), 2.79 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

STEP 6. 1-{1-[4-(2-azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl]}-2,2,2-trifluoroethanone

The title compound was prepared according to the procedure described in step 8 Example 1 from 1-{1-[4-(2-chloroethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}-2,2,2-trifluoroethanone (step 5).

¹H-NMR (CDCl₃) δ: 7.65 (1H, s), 7.46 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 7.06 (1H, s), 3.62 (2H, t, J=7.0 Hz), 3.02 (2H, t, J=7.0 Hz), 2.79 (2H, q, J=7.5 Hz), 1.35 (3H, t, J=7.5 Hz).

STEP 7. 1-{1-[4-(2-aminoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl]}-2,2,2-trifluoroethanone

The title compound was prepared according to the procedure described in step 9 of Example 1 from 1-{1-[4-(2-azidoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}-2,2,2-trifluoroethanone (step 6).

¹H-NMR (CDCl₃) δ: 7.65 (1H, s), 7.43 (2H, d, J=8.5 Hz), 7.28 (2H, d, J=8.5 Hz), 7.07 (2H, s), 3.09 (2H, t, J=6.7 Hz), 2.89 (2H, t, J=6.7 Hz), 2.79 (2H, q, J=7.4 Hz), 1.35 (3H, t, J=7.4 Hz).

STEP 8. *N*-{[(2-{4-[2-ethyl-5-(trifluoroacetyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 1-{1-[4-(2-aminoethyl)phenyl]-2-ethyl-1*H*-benzimidazol-5-yl}-2,2,2-trifluoroethanone (step 7).

MS (ESI) *m/z*: 547 (MH⁺), 545 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 7.72 (2H, d, J=8.4 Hz), 7.64 (1H, s), 7.39 (2H, d, J=8.4 Hz), 7.27-7.29 (4H, m), 7.02-7.04 (2H, m), 6.75 (1H, br.s), 3.55-3.62 (2H, m), 2.94 (2H, t, J=6.9 Hz), 2.79 (2H, q, J=7.5 Hz), 2.39 (3H, s), 1.33 (3H, t, J=7.5 Hz).

5 STEP 9. *N*-{[(2-{4-[2-ethyl-5-(trifluoroacetyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide *p*-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from *N*-{[(2-{4-[2-ethyl-5-(trifluoroacetyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (step 8)
10 m.p.: 194.1 °C.

IR (KBr) ν: 3589, 1701, 1627, 1521, 1458, 1330, 1091 cm⁻¹

EXAMPLE 352

15 2-{4-[2-ETHYL-5-(TRIFLUOROACETYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE *P*-TOLUENESULFONATE

STEP 1. 2-{4-[2-ethyl-5-(trifluoroacetyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 1-{2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazol-5-yl}-2,2,2-trifluoroethanone (Example 351, step 4).
20

MS (ESI) *m/z*: 548 (MH⁺), 546 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 7.93 (2H, d, J=8.4 Hz), 7.64 (1H, s), 7.28-7.35 (4H, m), 7.20 (2H, d, J=8.4 Hz), 7.05-7.07 (2H, m), 4.37 (2H, t, J=6.6 Hz), 3.00 (2H, t, J=6.6 Hz), 2.76 (2H, q, J=7.6 Hz), 2.43 (3H, s), 1.31 (3H, t, J=7.6 Hz).
25

STEP 2. 2-{4-[2-ethyl-5-(trifluoroacetyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate *p*-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from 2-{4-[2-ethyl-5-(trifluoroacetyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (Step 1)
m.p.: 92-97 °C.

- 5 IR (KBr) v: 1745, 1519, 1458, 1350, 1222, 1163, 1122 cm⁻¹

EXAMPLE 353

2-{4-[5-ACETYL-2-(1*H*-PYRAZOL-3-YL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE *P*-TOLUENESULFONATE

- 10 STEP 1. 1-[1-[4-(2-hydroxyethyl)phenyl]-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-5-yl]ethanone

The title compound was prepared according to the procedure described in step 1 of Example 236 from 1-(3-amino-4-[[4-(2-hydroxyethyl)phenyl]amino}phenyl)ethanone (Example 78, step 2).

- 15 MS (EI) m/z: 345 (M⁺)

¹H-NMR (CDCl₃) δ: 8.53 (1H, s), 7.94 (1H, d, J=8.4 Hz), 7.48-7.53 (3H, m), 7.37 (2H, d, J=8.2 Hz), 7.27 (1H, s), 7.18 (1H, d, J=8.4 Hz), 6.03 (1H, br.s), 4.02 (2H, t, J=6.6 Hz), 3.05 (2H, t, J=6.6 Hz), 2.69 (3H, s).

- STEP 2. 2-{4-[5-acetyl-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 1-[1-[4-(2-hydroxyethyl)phenyl]-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-5-yl]ethanone (step 1).

MS (ESI) m/z: 544 (MH⁺), 542 ([M-H]⁻)

- 25 ¹H-NMR (DMSO-d₆) δ: 8.41 (1H, s), 7.77-7.89 (4H, m), 7.38-7.42 (7H, m), 7.12 (1H, d, J=8.5 Hz), 6.65 (1H, br.s), 4.29 (2H, t, J=6.6 Hz), 2.96 (2H, t, J=6.6 Hz), 2.66 (3H, s), 2.35 (3H, s).

STEP 3. 2-{4-[5-acetyl-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate *p*-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from 2-{4-[5-acetyl-2-(1*H*-pyrazol-3-yl)-1*H*-benzimidazol-1-

- 5 yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (step 2)
m.p.: 204 °C.

IR (KBr) ν : 3249, 1755, 1676, 1595, 1517, 1440, 1332, 1207, 1161, 1008 cm^{-1}

EXAMPLE 354

N-{[(2-{4-[6-CHLORO-2-[1-(METHYLOXY)ETHYL]-5-

- 10 (TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-
METHYLBENZENESULFONAMIDE *P*-TOLUENESULFONATE

STEP 1. 2-(4-{[5-chloro-2-[(2-hydroxypropanoyl)amino]-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate

- 15 The title compound was prepared according to the procedure described in step 3 of Example 339 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2).

MS (EI) m/z : 444 (M^+)

STEP 2. 2-{4-[6-chloro-2-(1-hydroxyethyl)-5-(trifluoromethyl)-1*H*-

- 20 benzimidazol-1-yl]phenyl}ethyl acetate
- The title compound was prepared according to the procedure described in step 4 of Example 339 from 2-(4-{[5-chloro-2-[(2-hydroxypropanoyl)amino]-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (step 1)

- $^1\text{H-NMR}$ (CDCl_3) δ : 8.14 (1H, s), 7.48 (2H, d, $J=8.4$ Hz), 7.34 (2H, d, $J=8.4$ Hz), 7.24 (1H, s), 4.88-4.98 (1H, m), 4.38 (2H, t, $J=7.0$ Hz), 3.66 (1H, d, $J=8.1$ Hz), 3.08 (2H, t, $J=7.0$ Hz), 2.09 (3H, s), 1.57 (3H, d, $J=6.6$ Hz).

STEP 3. 1-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1*H*-

benzimidazol-2-yl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[6-chloro-2-(1-hydroxyethyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl acetate (step 2)

5 MS (ESI) m/z: 384 (M⁺)

¹H-NMR (CDCl₃) δ: 8.14 (1H, s), 7.49 (2H, d, J=8.6 Hz), 7.34 (2H, d, J=8.6 Hz), 7.25 (1H, s), 4.89-4.96 (1H, m), 3.98 (2H, t, J=6.2 Hz), 3.36 (1H, d, J=5.5 Hz), 3.01 (2H, t, J=6.2 Hz), 1.54 (3H, m).

STEP 4. 1-[6-chloro-1-[4-(2-1-(1,1-dimethylethyl)(diphenyl)silyl]oxy}ethyl)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-yl]ethanol

A mixture of 1-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-yl]ethanol (step 3, 461 mg, 1.19 mmol), *tert*-Butyldiphenylsilyl chloride (0.35 ml, 1.3 mmol), triethylamine (0.2 ml, 1.4 mmol) and N,N-dimethylaminopyridine (6 mg, 0.05 mmol) in dichloromethane (11 ml) was stirred under nitrogen at room temperature for 4 h. was added water (50 ml) and extracted with dichloromethane (100 ml). The organic layer was washed with water (50 ml), brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (3:1/1:1) to afford 590 mg (80%) of the title compound as white amorphous.

¹H-NMR (CDCl₃) δ: 8.14 (1H, s), 7.59-7.63 (4H, m), 7.34-7.46 (8H, m), 7.22-7.30 (3H, m), 4.87-4.96 (1H, m), 3.94 (2H, t, J=6.4 Hz), 3.29 (1H, d, J=8.1 Hz), 2.97 (2H, t, J=6.4 Hz), 1.52 (3H, d, J=6.6 Hz), 1.03 (9H, s).

STEP 5. 6-chloro-1-[4-(2-1-(1,1-dimethylethyl)(diphenyl)silyl]oxy}ethyl)phenyl]-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1H-benzimidazole

A solution of 1-[6-chloro-1-[4-(2-1-(1,1-dimethylethyl)(diphenyl)silyl]oxy}ethyl)phenyl]-5-(trifluoromethyl)-1H-

benzimidazol-2-yl]ethanol (step 4, 590 mg, 0.95 mmol) in DMF (10 ml) was added NaH (45 mg, 1.13 mmol). Then the mixture was added MeI (0.08 ml, 1.23 mmol) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was added water (30 ml) and extracted with ethyl acetate (100 ml). The organic layer was washed with water (50 ml), brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (3:1) to afford 550 mg (91%) of the title compound as colorless oil.

¹H-NMR (CDCl₃) δ: 8.17 (1H, s), 7.20-7.70 (15H, m), 4.54 (1H, q, J=6.6 Hz), 3.95 (2H, t, J=6.6 Hz), 3.22 (3H, s), 2.97 (2H, t, J=6.6 Hz), 1.55 (3H, d, J=6.6 Hz), 1.03 (9H, s).

STEP 6. 2-[4-[6-chloro-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethanol

The title compound was prepared according to the procedure described in step 6 of Example 90 from 6-chloro-1-[4-(2-[(1,1-dimethylethyl)(diphenyl)silyl]oxy)ethyl]phenyl]-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1H-benzimidazole (step 5).

MS (ESI) m/z: 398

¹H-NMR (CDCl₃) δ: 8.18 (1H, s), 7.49 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz), 7.24 (1H, s), 4.58 (1H, q, J=6.6 Hz), 4.00 (2H, br.s), 3.24 (3H, s), 3.02 (2H, t, J=6.5 Hz), 1.55-1.60 (3H, m).

STEP 7. 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step 7 of Example 1 from 2-[4-[6-chloro-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethanol (step 6).

MS (ESI) m/z: 416 (M⁺)

¹H-NMR (CDCl₃) δ: 8.18 (1H, s), 7.48 (2H, d, J=8.5 Hz), 7.35 (2H, d, J=8.5 Hz), 7.23 (1H, s), 5.57 (1H, q, J=6.6 Hz), 3.83 (2H, t, J=7.1 Hz), 3.19-3.24 (5H, m), 1.57 (3H, d, J=6.6 Hz).

STEP 8. 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step 8 of Example 1 from 6-chloro-1-[4-(2-chloroethyl)phenyl]-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1*H*-benzimidazole (step 7).

MS (ESI) m/z: 423 (M⁺)

¹H-NMR (CDCl₃) δ: 8.18 (1H, s), 7.48 (2H, d, J=8.2 Hz), 7.35 (2H, d, J=8.2 Hz), 7.22 (1H, s), 4.57 (1H, q, J=6.6 Hz), 3.63 (2H, t, J=6.9 Hz), 3.23 (3H, s), 3.04 (2H, t, J=6.9 Hz), 1.56 (3H, d, J=6.6 Hz).

STEP 9. 2-{4-[6-chloro-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethanamine

The title compound was prepared according to the procedure described in step 7 of Example 37 from 1-[4-(2-azidoethyl)phenyl]-6-chloro-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1*H*-benzimidazole (step 8).

¹H-NMR (CDCl₃) δ: 8.18 (1H, s), 7.45 (2H, d, J=8.4 Hz), 7.32 (2H, d, J=8.4 Hz), 7.24 (1H, s), 4.57 (1H, q, J=6.6 Hz), 3.23 (3H, s), 3.10 (2H, br.s), 2.90 (2H, t, J=6.6 Hz), 1.57 (3H, d, J=6.6 Hz).

STEP 10. *N*-{[(2-{4-[6-chloro-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in step 10 of Example 1 from 2-{4-[6-chloro-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethanamine (step 9).

MS (ESI) m/z: 595 (MH⁺), 593 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 8.18 (1H, s), 7.73 (2H, d, J=8.4 Hz), 7.42 (2H, d, J=8.6 Hz), 7.27-7.34 (4H, m), 7.21 (1H, s), 6.76 (1H, br.s), 4.57 (1H, q, J=6.6 Hz), 3.56-3.63 (2H, m), 3.23 (3H, s), 2.96 (2H, t, J=7.1 Hz), 2.41 (3H, s), 1.56 (3H, d, J=6.6 Hz).

5 STEP 11. *N*-{[(2-{4-[6-chloro-2-[1-(methyloxy)ethyl]-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide *p*-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from *N*-{[(2-{4-[6-chloro-2-[1-(methyloxy)ethyl]-5-

10 (trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (step 10)

IR (KBr) v: 2873, 1712, 1517, 1454, 1342, 1122, 1033, 1010 cm⁻¹

EXAMPLE 355

15 2-{4-[2-ETHYL-5-(1-HYDROXYETHYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE *P*-TOLUENESULFONATE

STEP 1. 2-{4-[2-ethyl-5-(1-hydroxyethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

20 The title compound was prepared according to the procedure described in Example 345 from 2-[4-(5-acetyl-2-ethyl-1*H*-benzimidazol-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate (Example 332)

MS (ESI) m/z: 508 (MH⁺), 506 ([M-H]⁻)

25 ¹H-NMR (CDCl₃) δ: 7.94 (2H, d, J=8.3 Hz), 7.77 (1H, s), 7.03-7.35 (8H, m), 5.04 (1H, q, J=6.4 Hz), 4.36 (2H, t, J=6.6 Hz), 2.97 (2H, t, J=6.6 Hz), 2.74 (2H, q, J=7.5 Hz), 2.43 (3H, s), 1.56 (3H, d, J=6.4 Hz), 1.28 (3H, t, J=7.5 Hz).

STEP 2. 2-{4-[2-ethyl-5-(1-hydroxyethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate *p*-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from 2-{4-[2-ethyl-5-(1-hydroxyethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (step 1)
m.p.: 96-110 °C.

- 5 IR (KBr) v: 1743, 1519, 1456, 1163, 1033, 1010 cm⁻¹

EXAMPLE 356

2-{4-[2-ETHYL-4-METHYL-5-(METHYLOXY)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE *P*-TOLUENESULFONATE

- 10 STEP 1. 2-(4-{[3-methyl-4-(methyloxy)-2-nitrophenyl]amino}phenyl)ethanol

The title compound was prepared according to the procedure described in step 3 of Example 1 from 1-chloro-3-methyl-4-(methyloxy)-2-nitrobenzene
MS (EI) m/z: 302 (M⁺)

- 15 ¹H-NMR (CDCl₃) δ: 7.11-7.20 (3H, m), 6.89-6.96 (3H, m), 6.53 (1H, br.s), 3.83 (5H, br.s), 2.81 (2H, t, J=6.4 Hz), 2.25 (3H, s).

STEP 2. 2-(4-{[2-amino-3-methyl-4-(methyloxy)phenyl]amino}phenyl)ethanol

The title compound was prepared according to the procedure described in step 4 of Example 1 from 2-(4-{[3-methyl-4-(methyloxy)-2-nitrophenyl]amino}phenyl)ethanol (step 1).

- 20 MS (EI) m/z: 272 (M⁺)

¹H-NMR (CDCl₃) δ: 7.03 (2H, d, J=8.6 Hz), 6.92 (1H, d, J=8.6 Hz), 6.57 (2H, d, J=8.6 Hz), 6.32 (2H, d, J=8.6 Hz), 5.01 (1H, br.s), 3.77-3.90 (7H, m), 2.76 (2H, t, J=6.4 Hz), 2.09 (3H, s).

STEP 3. 2-{4-[2-ethyl-4-methyl-5-(methyloxy)-1*H*-benzimidazol-1-yl]phenyl}ethyl propanoate

- 25

The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-(4- {[2-amino-3-methyl-4-(methyloxy)phenyl]amino}phenyl)ethanol (step 2).

MS (EI) m/z: 366 (M^+)

5 STEP 4. 2-{4-[2-ethyl-4-methyl-5-(methyloxy)-1*H*-benzimidazol-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-{4-[2-ethyl-4-methyl-5-(methyloxy)-1*H*-benzimidazol-1-yl]phenyl}ethyl propanoate (step 3).

¹H-NMR (CDCl₃) δ: 7.42 (2H, d, =8.1 Hz), 7.27 (2H, d, J=8.1 Hz), 6.84 (2H, s),
10 3.97 (2H, t, J=6.4 Hz), 3.86 (3H, s), 2.99 (2H, t, J=6.4 Hz), 2.81 (2H, q, J=7.7 Hz), 2.58 (3H, s), 1.26 (3H, t, J=7.7 Hz).

STEP 5. 2-{4-[2-ethyl-4-methyl-5-(methyloxy)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described
15 in Example 3 from 2-{4-[2-ethyl-4-methyl-5-(methyloxy)-1*H*-benzimidazol-1-yl]phenyl}ethanol (step 4).

MS (ESI) m/z: 508 (MH^+), 506 ($[M-H]^+$)

¹H-NMR (CDCl₃) δ: 7.98 (2H, d, J=8.3 Hz), 7.33 (2H, d, J=8.9 Hz), 6.88-6.91 (6H, m), 4.28 (2H, t, J=6.0 Hz), 3.89 (3H, s), 2.84 (2H, t, J=6.0 Hz), 2.74 (2H, q,
20 J=7.5 Hz), 2.56 (3H, s), 2.43 (3H, s), 1.05 (3H, t, J=7.5 Hz).

STEP 6. 2-{4-[2-ethyl-4-methyl-5-(methyloxy)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate *p*-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from 2-{4-[2-ethyl-4-methyl-5-(methyloxy)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (step 5)

m.p.: 94-103 °C.

IR (KBr) ν: 1747, 1458, 1232, 1163, 1120 cm⁻¹

EXAMPLE 3572-[4-(2-ETHYL-5-PHENYL-1H-BENZIMIDAZOL-1-
YL)PHENYL]ETHYL(4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 2-{4-[(4-bromo-2-nitrophenyl)amino]phenyl}ethanol

- 5 The title compound was prepared according to the procedure described in step 1 of Example 162 from 2,5-dibromonitrobenzene.

¹H-NMR (CDCl₃) δ: 9.43 (1H, br.s), 8.34 (1H, d, J=2.4 Hz), 7.43-7.39 (1H, m), 7.30 (2H, d, J=8.3 Hz), 7.20 (2H, d, J=8.3 Hz), 7.08 (1H, d, J=9.2 Hz), 3.94-3.88 (2H, m), 2.90 (2H, d, J=6.4 Hz), 1.43 (1H, t, J=5.7 Hz).

10 STEP 2. 2-{4-[(2-amino-4-bromophenyl)amino]phenyl}ethanol

 The title compound was prepared according to the procedure described in step 2 of Example 28 from 2-{4-[(4-bromo-2-nitrophenyl)amino]phenyl}ethanol (step 1).

- ¹H-NMR (CDCl₃) δ: 7.08 (2H, d, J=8.4 Hz), 6.97-6.93 (2H, m), 6.84 (1H, dd, J=8.3, 2.2 Hz), 6.69 (2H, d, J=8.6 Hz), 5.04 (1H, br.s), 3.80 (2H, br.s), 3.82 (2H, t, J=6.4 Hz), 2.79 (2H, t, J=6.4 Hz).
- 15

STEP 3. 2-[4-(5-bromo-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate

- The title compound was prepared according to the procedure described in step 5 of Example 1 from 2-{4-[(2-amino-4-bromophenyl)amino]phenyl}ethanol (step 2).
- 20
- MS (EI) m/z 401 (M⁺)

STEP 4. 2-[4-(5-bromo-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol

- The title compound was prepared according to the procedure described in step 6 of Example 1 from 2-[4-(5-bromo-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl propionate (step 3).
- 25

09977781.101501

¹H-NMR (CDCl₃) δ: 7.90 (1H, s), 7.45 (2H, d, J=8.1 Hz), 7.26-7.30 (3H, m), 6.96 (1H, d, J=8.4 Hz), 3.98 (2H, m), 3.00 (2H, t, J=6.4 Hz), 2.78 (2H, q, J=7.6 Hz), 1.34 (3H, t, J=7.6 Hz).

STEP 5. 2-[4-(2-ethyl-5-phenyl-1H-benzimidazol-1-yl)phenyl]ethanol

To a solution of 2-[4-(5-bromo-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 4, 116 mg, 0.57 mmol) in 1,2-dimethoxyethane (DME, 6 ml) was added PhB(OH)₂ (141 mg, 1.16 mmol), K₂CO₃ (240 mg, 1.75 mmol) and Pd(PPh₃)₄ (67 mg, 0.06 mmol). This mixture was stirred at 95 °C for 11 h. The reaction mixture was diluted with water and extracted with CH₂Cl₂ (4 x 10 ml). The organic layer was dried (MgSO₄) and concentrated to give brown oil. This mixture was purified by SiO₂ preparative TLC (hexane / ethyl acetate = 1 / 5) to afford 52 mg (27%) of the title compound.

MS (EI) m/z 342 (M⁺)

¹H-NMR (CDCl₃) δ: 8.00 (1H, d, J=1.6 Hz), 7.65 (2H, dd, J=1.6, 8.4 Hz), 7.42-7.48 (5H, m), 7.32-7.35 (3H, m), 7.15 (2H, d, J=8.4 Hz), 4.00 (2H, brt), 3.01 (2H, t, J=6.5 Hz), 2.82 (2H, q, J=7.6 Hz), 1.37 (3H, t, J=7.6 Hz).

STEP 6. 2-[4-(2-ethyl-5-phenyl-1H-benzimidazol-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-[4-(2-ethyl-5-phenyl-1H-benzimidazol-1-yl)phenyl]ethanol (step 5).

MS (ESI) m/z 540 [M + H]⁺, 538 [M - H]⁻.

¹H-NMR (CDCl₃) δ: 8.00 (1H, s), 7.94 (2H, d, J=8.2 Hz), 7.65 (2H, d, J=8.6 Hz), 7.43-7.48 (3H, m), 7.29-7.36 (7H, m), 7.15 (2H, d, J=8.4 Hz), 4.39 (2H, t, J=6.8 Hz), 3.01 (2H, t, J=6.4 Hz), 2.70 (2H, q, J=7.4 Hz), 2.43 (s, 3H), 1.35 (3H, t, J=7.6 Hz).

EXAMPLE 358

2-{4-[2-ETHYL-5-(5-PYRIMIDINYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 2-{4-[2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-
benzimidazol-1-yl]phenyl}ethanol

- 5 To a solution of 2-[4-(5-bromo-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethanol (Example 357 step 4, 2.5 g, 7.24 mmol) and bis(pinacolato)diboron (1.84 g, 7.24 mmol) in DMSO was added KOAc (2.13 g, 21.7 mmol), 1,1'-Bis(diphenylphosphino)ferrocene (241 mg, 0.43 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (362 mg, 0.44 mmol). This mixture was stirred at 80 °C for
- 10 7 h. The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 80 ml). The organic layer was washed with brine, dried (MgSO₄) and concentrated to give black oil. This mixture was purified by neutral SiO₂ chromatography eluting with hexane / ethyl acetate (1:4) to afford 1.38 g (35%) of the title compound as pink solids.
- 15 MS (EI) m/z 391 [M - H]⁺
¹H-NMR (CDCl₃) δ: 8.25 (1H, s), 7.64 (2H, dd, J=0.8, 8.1 Hz), 7.45 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz), 7.08 (1H, d, J=8.1 Hz), 3.99 (2H, t, J=6.5 Hz), 3.00 (2H, t, J=6.5 Hz), 2.81 (2H, q, J=7.6 Hz), 1.36 (12H, s), 1.32 (3H, t, J=7.8 Hz).
- 20 STEP 2. 2-{4-[2-ethyl-5-(5-pyrimidinyl)-1H-benzimidazol-1-yl]phenyl}ethanol
To a solution of 2-[4-[2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzimidazol-1-yl]phenyl]ethanol (step 1, 100 mg, 0.26 mmol) and 5-bromopyrimidine (45 mg, 0.28 mmol) in 1,2-dimethoxyethane (3.5 ml) was added sat. NaHCO₃ aq. (1.2 ml) and Pd(PPh₃)₄ (60 mg, 0.05 mmol). This
- 25 mixture was stirred at 70 °C for 17 h. The reaction mixture was diluted with water and extracted with CH₂Cl₂ (3 x 10 ml). The organic layer was dried (MgSO₄) and concentrated to give light brown oil. This mixture was purified by

SiO₂ preparative TLC (CH₂Cl₂ / methanol = 10 / 1) to afford 45 mg (50%) of the title compound.

MS (EI) m/z 344 (M⁺)

¹H-NMR (CDCl₃) δ: 9.19 (1H, s), 9.00(2H, s), 7.99 (1H, s), 7.49 (2H, d, J=8.2 Hz), 7.31-7.42 (3H, m), 7.23 (1H, d, J=8.4 Hz), 4.00 (2H, q, J=6.1 Hz), 3.02 (2H, t, J=6.4 Hz), 2.83 (2H, q, J=7.6 Hz), 1.39 (3H, t, J=7.6 Hz).

STEP 3. 2-{4-[2-ethyl-5-(5-pyrimidinyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[2-ethyl-5-(5-pyrimidinyl)-1H-benzimidazol-1-yl]phenyl}ethanol (step 2).

MS (ESI) m/z 542 [M + H]⁺, 540 [M - H]⁻.

¹H-NMR (CDCl₃) δ: 9.20 (1H, s), 8.97 (2H, s), 7.30-7.42 (4H, m), 7.24 (2H, d, J= 8.2 Hz), 7.14 (2H, d, J=8.2 Hz), 4.41 (2H, t, J=6.4 Hz), 3.03 (2H, t, J= 6.1 Hz), 2.89 (2H, q, J=7.4 Hz), 2.43 (3H, s), 1.34 (3H, t, J=7.4 Hz).

EXAMPLE 359

2-{4-[2-ETHYL-5-(4-PYRIDINYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[2-ethyl-5-(4-pyridinyl)-1H-benzimidazol-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in step 1 of Example 358 from 4-bromopyridine hydrochloride (step 2).

MS (EI) m/z 343 (M⁺).

¹H-NMR (CDCl₃) δ: 8.66 (2H, d, J=6.1 Hz), 8.07 (1H, d, J=1.2 Hz), 7.57 (2H, d, J=6.1 Hz), 7.45-7.52 (3H, m), 7.34 (2H, d, J=8.4 Hz), 7.20 (1H, d, J= 8.4 Hz), 4.00 (2H, br.s), 3.03 (2H, t, J=6.6 Hz), 2.83 (2H, q, J=7.4 Hz), 1.39 (3H, t, J=7.4 Hz).

STEP 2. 2-{4-[2-ethyl-5-(4-pyridinyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[2-ethyl-5-(4-pyridinyl)-1H-benzimidazol-1-

5 yl]phenyl} ethanol (step 1).

MS (ESI) m/z 541 [M + H]⁺, 539 [M - H]⁻.

¹H-NMR (CDCl₃) δ: 8.52 (2H, d, J=5.8 Hz), 8.00 (1H, s), 7.94 (2H, d, J=8.1 Hz), 7.48 (2H, d, J= 5.8 Hz), 7.23-7.40 (5H, m), 7.20 (2H, d, J=8.1 Hz), 7.00 (2H, d, J=8.2 Hz), 4.41 (2H, t, J=5.8 Hz), 3.02 (2H, t, J= 5.8 Hz), 2.76 (2H, q, J=7.4 Hz), 2.39 (3H, s), 1.32 (3H, t, J=7.4 Hz).

EXAMPLE 360

2-{4-[2-ETHYL-5-(3-PYRIDINYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 2-{4-[2-ethyl-5-(3-pyridinyl)-1H-benzimidazol-1-yl]phenyl} ethanol

The title compound was prepared according to the procedure described in step 1 of Example 358 from 3-bromopyridine.

MS (EI) m/z 343 (M)⁺.

¹H-NMR (CDCl₃) δ: 8.91 (1H, d, J=1.8 Hz), 8.55-8.61 (1H, m), 8.00 (1H, s), 7.90-7.97 (1H, m), 7.48 (2H, d, J=8.2 Hz), 7.42 (1H, d, J=8.7 Hz), 7.35 (2H, d, J=8.2 Hz), 7.21 (1H, d, J=8.4 Hz), 4.00 (2H, m), 3.02 (2H, t, J=6.5 Hz), 2.83 (2H, q, J=7.6 Hz), 1.92 (1H, s), 1.39 (3H, t, J=7.6 Hz).

STEP 2. 2-{4-[2-ethyl-5-(3-pyridinyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from 2-{4-[2-ethyl-5-(3-pyridinyl)-1H-benzimidazol-1-

yl]phenyl} ethanol (step 1).

MS (ESI) m/z 541 [M + H]⁺, 539 [M - H]⁻.

¹H-NMR (CDCl₃) δ: 8.76 (1H, s), 8.63 (1H, m), 7.87-8.01 (4H, m), 7.22-7.50 (6H, m), 7.23-7.40 (5H, m), 7.16 (2H, d, J=8.2 Hz), 7.00 (1H, d, J=8.2 Hz), 4.42 (2H, br.s), 3.01 (2H, br.s), 2.74 (2H, q, J=7.4 Hz), 2.43 (3H, s), 1.31 (3H, t, J=7.4 Hz).

5 EXAMPLE 361

2-{4-[2-ETHYL-5-(2-PYRIDINYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 2-{4-[2-ethyl-5-(2-pyridinyl)-1H-benzimidazol-1-yl]phenyl}ethanol

The title compound was prepared according to the procedure described in
10 step 1 of Example 358 from 2-bromopyridine.

MS (EI) m/z 343 (M)⁺.

¹H-NMR (CDCl₃) δ: 8.70 (1H, dd, J=1.5, 5.3 Hz), 8.32 (1H, d, J=1.5 Hz), 8.00 (1H, dd, J=1.5, 8.4 Hz), 7.76-7.80 (2H, m), 7.48 (2H, d, J=8.2 Hz), 7.35 (2H, d, J=8.2 Hz), 7.16-7.23 (2H, m), 3.93-4.05 (2H, m), 3.01 (2H, t, J=6.6 Hz), 2.83
15 (2H, q, J=7.6 Hz), 1.91 (1H, s), 1.38 (3H, t, J=7.6 Hz).

STEP 2. 2-{4-[2-ethyl-5-(2-pyridinyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-
methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in
Example 3 from 2-{4-[2-ethyl-5-(2-pyridinyl)-1H-benzimidazol-1-
20 yl]phenyl}ethanol (step 1).

MS (ESI) m/z 541 [M + H]⁺, 539 [M - H]⁻.

¹H-NMR (CDCl₃) δ: 8.68 (1H, d, J=4.6 Hz), 8.31 (1H, s), 7.88-7.98 (3H, m),
7.73-7.82 (2H, m), 7.17-7.26 (5H, m), 7.07-7.17 (3H, m), 4.29 (2H, t, J=6.3 Hz),
2.90 (2H, t, J=6.4 Hz), 2.73 (2H, q, J=7.6 Hz), 2.36 (3H, s), 1.28 (3H, t, J=7.6
25 Hz).

EXAMPLE 362

2-{4-[2-ETHYL-5-(4-PYRIDINYL)-1H-BENZIMIDAZOL-1-
YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE
STEP 1. 2-{4-[2-ethyl-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzimidazol-1-
yl]phenyl}ethanol

- 5 The title compound was prepared according to the procedure described in step 1 of Example 358 from 4-bromo-1-methyl-1H-pyrazole (Huettel et al., *Liebigs Ann. Chem.*, 1955, 593, 179).

MS (EI) m/z 343 (M⁺)

- ¹H-NMR (CDCl₃) δ: 7.86 (1H, s), 7.78 (1H, s), 7.46 (2H, d, J=8.4 Hz), 7.28 -
10 7.35 (3H, m), 7.09 (2H, d, J=8.2 Hz), 3.99 (2H, m), 3.01 (2H, t, J=6.4 Hz), 2.81 (2H, q, J=7.6 Hz), 1.36 (3H, t, J=7.6 Hz).

STEP 2. 2-{4-[2-ethyl-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzimidazol-1-
yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

- The title compound was prepared according to the procedure described in
15 Example 3 from 2-{4-[2-ethyl-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzimidazol-1-yl]phenyl}ethanol (step 1).

MS(ESI) m/z 544 [M + H]⁺, 542 [M - H]⁻.

- ¹H-NMR (CDCl₃) δ: 7.95 (1H, s), 7.92 (1H, s), 7.86 (4H, m), 7.77 (1H, s), 7.62 (1H, s), 7.24-7.40 (7H, m), 7.06 (2H, d, J=7.7 Hz), 4.39 (2H, t, J=6.0 Hz), 3.97
20 (3H, s), 3.02 (2H, q, J=6.3 Hz), 2.78 (2H, q, J=7.4 Hz), 2.44 (3H, s), 1.35 (3H, t, J=7.4 Hz).

EXAMPLE 363

- 2-{4-[6-CHLORO-2-[3-OXO-3-(1-PYRROLIDINYL)PROPYL]-5-
(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-
25 METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in Example 339 from 2-(4-{[2-amino-5-chloro-4-

(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2) and 4-oxo-4-(1-pyrrolidinyl)butanoic acid (McCasland; Proskow, *J. Org. Chem.*, 1957, 22, 122.).
m.p.: 98-105 °C.

- 5 IR (KBr) v: 2875, 1747, 1624, 1517, 1400, 1346, 1130, 1085 cm⁻¹
MS (ESI) m/z: 663 (MH⁺), 661 ([M-H]⁻)
¹H-NMR (CDCl₃) δ: 8.08 (1H, s), 7.92 (2H, d, J=8.2 Hz), 7.22-7.36 (7H, m), 4.38 (2H, t, J=6.6 Hz), 3.49 (2H, t, J=6.8 Hz), 3.43 (2H, t, J=6.8 Hz), 2.97-3.07 (4H, m), 2.88 (2H, m), 2.44 (3H, s), 1.94-1.98 (2H, m), 1.82-1.86 (2H, m).

10 EXAMPLE 364

2-[4-[6-CHLORO-2-[3-OXO-3-(1-PIPERIDINYL)PROPYL]-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in

- 15 Example 339 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2) and 4-oxo-4-(1-piperidinyl)butanoic acid (Becker, Frederick F.; Banik, Bimal K., *Bioorg. Med. Chem. Lett.*, 1998, 20, 2877).
m.p.: 210 °C.

- 20 IR (KBr) v: 1753, 1649, 1515, 1433, 1406, 1366, 1161, 1118, 1091 cm⁻¹
MS (ESI) m/z: 677 (MH⁺), 675 ([M-H]⁻)
¹H-NMR (CDCl₃) δ: 8.14 (1H, s), 7.78 (2H, d, J=8.4 Hz), 7.47-7.56 (4H, m), 7.42 (2H, d, J=8.4 Hz), 7.31 (1H, s), 4.29 (2H, t, J=6.6 Hz), 3.37-3.40 (4H, m), 2.92-2.99 (6H, m), 2.36 (3H, s), 1.50-1.56 (4H, m), 1.35-1.36 (2H, m).

25 EXAMPLE 365

2-{4-[6-CHLORO-2-[3-(2-OXO-1-PYRROLIDINYL)PROPYL]-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

The title compound was prepared according to the procedure described in

- 5 Example 339 from 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2) and 4-(2-oxo-1-pyrrolidinyl)butanoic acid (Miyano, Seiji; Fujii, Shinichiro; Yamashita, Osamu; Toraishi, Naoko; Sumoto, Kunihiro, *J. Heterocycl. Chem.*, 1982, 19, 1465).

- 10 m.p.: 85-90 °C.

IR (KBr) v: 1745, 1624, 1517, 1433, 1348, 1299, 1161, 1130, 1085 cm⁻¹

MS (ESI) m/z: 663 (MH⁺), 661 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 8.09 (1H, s), 7.91 (2H, d, J=8.5 Hz), 7.19-7.33 (7H, m), 4.42 (2H, t, J=6.0 Hz), 3.38 (2H, t, J=7.0 Hz), 3.27 (2H, t, J=7.0 Hz), 3.00 (2H, t, J=6.0 Hz), 2.70-2.75 (2H, m), 2.42 (3H, s), 2.37-2.40 (2H, m), 1.93-2.04 (4H, m).

- 15

EXAMPLE 366

2-{4-[6-CHLORO-2-[3-(2-OXO-1-PIPERIDINYL)PROPYL]-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE

- 20

The title compound was prepared according to the procedure described in Example 339 from 2-(4-{[2-amino-5-chloro-4-

(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2) and 4-(2-oxo-1-piperidinyl)butanoic acid (Miyano, Seiji; Fujii, Shinichiro;

- 25 Yamashita, Osamu; Toraishi, Naoko; Sumoto, Kunihiro, *J. Heterocycl. Chem.*, 1982, 19, 1465).

m.p.: 98-105 °C.

IR (KBr) ν : 1745, 1618, 1433, 1348, 1301, 1230, 1161, 1130, 1085 cm^{-1}

MS (ESI) m/z : 677 (MH^+), 675 ($[\text{M}-\text{H}]^-$)

^1H -NMR (CDCl_3) δ : 8.08 (1H, s), 7.89 (2H, d, $J=8.0$ Hz), 7.16-7.29 (7H, m), 4.40 (2H, t, $J=5.9$ Hz), 3.35 (2H, t, $J=7.2$ Hz), 3.25-3.27 (2H, m), 2.98 (2H, t, $J=5.9$ Hz), 2.73 (2H, t, $J=7.2$ Hz), 2.35-2.40 (5H, m), 1.92-1.99 (2H, m), 1.73 – 1.76 (4H, m) .

EXAMPLE 367

N-{[(2-{4-[6-chloro-2-(1-hydroxyethyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide
step 1. 1-[6-chloro-1-[4-(2-chloroethyl)phenyl]-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]ethanol

The title compound was prepared according to the procedure described in Example 339, step 3 & Example 1, step 5 from 4-chloro-*N*²-[4-(2-chloroethyl)phenyl]-5-(trifluoromethyl)-1,2-benzenediamine and lactic acid.

^1H -NMR (CDCl_3) δ : 8.14 (1H, s), 7.49 (2H, d, $J=8.2$ Hz), 7.37 (2H, d, $J=8.2$ Hz), 4.90-4.96 (1H, m), 3.83 (2H, t, $J=6.8$ Hz), 3.75 (1H, d, $H=8.1$ Hz), 3.22 (2H, t, $J=6.8$ Hz), 1.57 (3H, d, $J=6.9$ Hz).

step 2. *N*-{[(2-{4-[6-chloro-2-(1-hydroxyethyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in Example 1 from 1-[6-chloro-1-[4-(2-chloroethyl)phenyl]-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]ethanol (step 1).

m.p.: 220 °C.

IR (KBr) ν : 3348, 1706, 1533, 1519, 1434, 1344, 1328, 1126 cm^{-1}

MS (ESI) m/z : 581 (MH^+), 579 ($[\text{M}-\text{H}]^-$)

¹H-NMR (CDCl₃) δ: 8.23 (1H, s), 7.78 (2H, d, J=8.1 Hz), 7.32-7.50 (7H, m), 6.58 (1H, br.s), 5.66 (1H, br.s), 4.78 (1H, br.s), 3.30-3.32 (2H, m), 2.79-2.82 (2H, m), 2.34 (3H, s), 1.51 (3H, d, J=6.8 Hz).

EXAMPLE 368

5 *N*-{[(2-{4-[2-ACETYL-6-CHLORO-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE

step 1. 1-[6-chloro-1-[4-(2-chloroethyl)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-yl]ethanone

10 A solution of 1-[6-chloro-1-[4-(2-chloroethyl)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-yl]ethanol (Example 367, step 1, 400 mg, 1 mmol) in CH₂Cl₂ was added MnO₂ (2.7 g, 32 mmol). The mixture was stirred at room temperature for 24 h. This was directly purified by flash column chromatography eluting with hexane/ethyl acetate (4:1) to afford 350 mg (88%)
15 of the title compound as white solids.

¹H-NMR (CDCl₃) δ: 8.31 (1H, s), 7.44 (2H, d, J=8.1 Hz), 7.23-7.28 (3H, m), 3.82 (2H, t, J=7.3 Hz), 3.21 (2H, t, J=7.3 Hz), 2.80 (3H, s).

step 2. *N*-{[(2-{4-[2-acetyl-6-chloro-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

20 The title compound was prepared according to the procedure described in Example 1 from 1-[6-chloro-1-[4-(2-chloroethyl)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-yl]ethanone (step 1)

m.p.: 225 °C.

IR (KBr) ν: 3350, 1697, 1519, 1326, 1294, 1134, 1083 cm⁻¹

25 MS (ESI) m/z: 579 (MH⁺), 577 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 8.31 (1H, s), 7.74 (2H, d, J=8.4 Hz), 7.21-7.39 (7H, m), 6.70 (1H, br.s), 3.55-3.62 (2H, m), 2.94 (2H, t, J=7.2 Hz), 2.81 (3H, s), 2.40 (3H, s).

EXAMPLE 369

- 5 *N*-{[(2-{4-[6-CHLORO-2-(1-HYDROXY-1-METHYLETHYL)-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE

step 1. 2-[6-chloro-1-[4-(2-chloroethyl)phenyl]-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]-2-propanol

The title compound was prepared according to the procedure described in Example 339, step 3 & Example 1, step 5 from 2-hydroxyisobutyric acid and 4-chloro-*N*²-[4-(2-chloroethyl)phenyl]-5-(trifluoromethyl)-1,2-benzenediamine.

¹H-NMR (CDCl₃) δ: 8.13 (1H, s), 7.46 (2H, d, J=8.2 Hz), 7.34 (2H, d, J=8.2 Hz), 7.00 (1H, s), 3.84 (2H, t, J=7.0 Hz), 3.38 (1H, s), 3.22 (2H, t, J=7.00 Hz), 1.53 (6H, s).

step 2. *N*-{[(2-{4-[6-chloro-2-(1-hydroxy-1-methylethyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in Example 1 from 2-[6-chloro-1-[4-(2-chloroethyl)phenyl]-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]-2-propanol (step 1).

¹H-NMR (CDCl₃) δ: 8.13 (1H, s), 7.73 (2H, d, J=8.2 Hz), 7.30-7.39 (6H, m), 6.99 (1H, s), 6.68 (1H, br.s), 3.55-3.66 (2H, m), 2.95 (2H, t, J=6.6 Hz), 2.42 (3H, s), 1.13 (6H, d, J=6.2 Hz).

EXAMPLE 370

N-{[(2-{4-[6-CHLORO-2-(1-HYDROXY-1-METHYLETHYL)-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE MONO P-TOLUENESULFONATE

- 5 The title compound was prepared according to the procedure described in Example 231 from *N*-{[(2-{4-[6-chloro-2-(1-hydroxy-1-methylethyl)-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (Example 369).

m.p.: 146-150 °C.

- 10 IR (KBr) v: 1685, 1515, 1448, 1340, 1124, 1089, 1010 cm⁻¹

EXAMPLE 371

N-{1-[6-CHLORO-1-(4-{2-[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL}-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-2-

- 15 YL]ETHYL}ACETAMIDE
step 1. 1,1-dimethylethyl 1-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]ethylcarbamate

The title compound was prepared according to the procedure described in Example 339, step 3 & Example 1, step 5 from *N*-(*tert*-butoxycarbonyl)-alanine and 2-(4-{[2-amino-5-chloro-4-(trifluoromethyl)phenyl]amino}phenyl)ethyl acetate (Example 339, step 2).

MS (EI) m/z: 483 (M⁺)

¹H-NMR (CDCl₃) δ: 8.12 (1H, s), 7.50 (2H, d, J=8.6 Hz), 7.35-7.37 (2H, m), 7.24 (1H, s), 5.46 (1H, br.s), 4.92-4.98 (1H, m), 3.95-4.02 (2H, m), 3.00 (2H, t,

- 25 J=6.5 Hz), 1.43 (3H, s), 1.40 (9H, s).

03977751.101501

step 2. 1,1-dimethylethyl 1-[6-chloro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]ethylcarbamate

The title compound was prepared according to the procedure described in

- 5 Example 1 from 1,1-dimethylethyl 1-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]ethylcarbamate (step 1)

¹H-NMR (CDCl₃) δ: 8.13 (1H, s), 7.79 (2H, d, J=8.2 Hz), 7.15-7.35 (7H, m), 6.50 (1H, br.s), 5.55 (1H, d, J=8.6 Hz), 4.88-4.93 (1H, m), 3.46-3.52 (2H, m), 2.87-2.96 (2H, m), 2.41 (3H, s), 1.40 (12H, s).

- 10 step 3. *N*-{[(2-{4-[2-(1-aminoethyl)-6-chloro-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

A solution of 1,1-dimethylethyl 1-[6-chloro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]ethylcarbamate (step 2, 190 mg, 0.28 mmol) in CH₂Cl₂ (2 ml) was added trifluoroacetic acid (1 ml) and stirred at room temperature for 2 h. The mixture was added water (10 ml) and extracted with CH₂Cl₂ (20 ml). The organic layer was washed with brine (10 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with CH₂Cl₂/MeOH (10:1:5:1) to afford 160 mg (99%) of the title compound as white solids.

MS (ESI) *m/z*: 580 (MH⁺), 578 ([M-H]⁻)

step 4. *N*-{1-[6-chloro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]ethyl}acetamide

- 25 A mixture of *N*-{[(2-{4-[2-(1-aminoethyl)-6-chloro-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (step 3, 100 mg, 0.17 mmol) in CH₂Cl₂ (12 ml) was

added acetyl chloride (0.01 ml, 0.18 mmol) and stirred at room temperature for 5 h. The mixture was added water (10 ml) and extracted with CH₂Cl₂ (20 ml). The organic layer was washed with brine (10 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column

- 5 chromatography eluting with CH₂Cl₂/MeOH (10:1) to afford 59 mg (53%) of the title compound as white solids.

MS (ESI) m/z: 622 (MH⁺), 620 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 8.14 (1H, s), 7.80 (2H, d, J=8.2 Hz), 7.25-7.40 (7H, m), 7.00 (1H, br.s), 6.03 (1H, br.s), 5.15-5.20 (1H, m), 3.43-3.68 (2H, m), 2.88-2.98 (2H, m), 2.39 (3H, s), 1.96 (3H, s), 1.51 (3H, d, J=6.9 Hz).

EXAMPLE 372

N-{1-[6-chloro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl}ethyl}acetamide mono p-toluenesulfonate

The title compound was prepared according to the procedure described in Example 231 from *N*-{1-[6-chloro-1-(4-{2-[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl}ethyl}acetamide (Example 371).

m.p.: 135-142 °C.

IR (KBr) v: 3267, 1676, 1517, 1456, 1236, 1163, 1122, 1010 cm⁻¹

EXAMPLE 373

2-{4-[2-ethyl-5-(phenylcarbonyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonyl carbamate

step 1. (3-amino-4-{4-(2-hydroxyethyl)phenyl}amino)phenyl(phenyl)methanone

The title compound was prepared according to the procedure described in Example 78 from (4-chloro-3-nitrophenyl)(phenyl)methanone.

¹H-NMR (CDCl₃) δ: 7.77 (2H, d, J=6.9 Hz), 7.42-7.55 (3H, m), 7.36 (1H, s), 7.14-7.25 (4H, m), 6.97 (2H, d, J=8.5 Hz), 5.64 (1H, s), 3.83-3.89 (2H, m), 3.64 (2H, br.s), 2.84 (2H, t, J=6.6 Hz), 1.47 (1H, br.s).

step 2. {2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazol-5-yl}(phenyl)methanone

The title compound was prepared according to the procedure described in Example 1 from (3-amino-4-{[4-(2-hydroxyethyl)phenyl]amino}phenyl)(phenyl)methanone (step 1).

¹H-NMR (CDCl₃) δ: 8.21 (1H, s), 7.80-7.84 (3H, m), 7.44-7.57 (5H, m), 7.27-7.34 (2H, m), 7.18 (1H, d, J=8.4 Hz), 3.98-4.03 (2H, m), 3.02 (2H, t, =6.3 Hz), 2.81 (2H, q, J=7.6 Hz), 1.89 (1H, t, J=5.4 Hz), 1.37 (3H, t, J=7.6 Hz).

step 3. 2-{4-[2-ethyl-5-(phenylcarbonyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in Example 3 from {2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazol-5-yl}(phenyl)methanone (step 2).

MS (ESI) m/z: 568 (MH⁺), 566 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 8.21 (1H, s), 7.92 (2H, d, J=8.4 Hz), 7.79-7.84 (3H, m), 7.44-7.58 (3H, m), 7.23-7.36 (6H, m), 7.15 (1H, d, J=8.6 Hz), 4.37 (2H, t, J=6.6 Hz), 3.01 (2H, t, J=6.6 Hz), 2.79 (2H, q, J=7.6 Hz), 2.42 (3H, s), 1.34 (3H, t, J=7.6 Hz).

EXAMPLE 374

2-{4-[2-ETHYL-5-(PHENYLCARBONYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE MONO P-TOLUENESULFONATE

The title compound was prepared according to the procedure described in Example 231 from 2-{4-[2-ethyl-5-(phenylcarbonyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate (Example 373).
m.p.: 102-107 °C.

- 5 IR (KBr) v: 1747, 1654, 1517, 1448, 1033, 1008 cm⁻¹

EXAMPLE 375

N-{[(2-{4-[2-ETHYL-5-(PHENYLCARBONYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE

- 10 step 1. *N*-{[(2-{4-[2-ethyl-5-(phenylcarbonyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide

The title compound was prepared according to the procedure described in Example 78 from {2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazol-5-yl}(phenyl)methanone (Example 373, step 2).

- 15 MS (ESI) m/z: 567 (MH⁺), 565 ([M-H]⁻)

¹H-NMR (CDCl₃) δ: 8.20 (1H, s), 7.72-7.83 (5H, m), 7.28-7.60 (9H, m), 7.15 (1H, d, J=8.6 Hz), 6.74 (1H, br.s), 3.59 (2H, m), 2.94 (2H, t, J=7.1 Hz), 2.82 (2H, q, J=7.4 Hz), 2.39 (3H, s), 1.35 (3H, t, J=7.4 Hz).

EXAMPLE 376

- 20 *N*-{[(2-{4-[2-ETHYL-5-(PHENYLCARBONYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL)AMINO]CARBONYL}-4-METHYLBENZENESULFONAMIDE MONO P-TOLUENESULFONATE

The title compound was prepared according to the procedure described in Example 231 from *N*-{[(2-{4-[2-ethyl-5-(phenylcarbonyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (Example 375).

- 25 m.p.: 198 °C.

IR (KBr) v: 1697, 1660, 1596, 1519, 1446, 1319, 1035 cm⁻¹

EXAMPLE 377

2-{4-[2-[1-(ACETYLAMINO)-1-METHYLETHYL]-6-CHLORO-5-(TRIFLUOROMETHYL)-1H-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-

5 METHYLPHENYL)SULFONYLCARBAMATE

STEP 1. 2-{4-[6-chloro-2-(1-chloro-1-methylethyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl acetate

To a solution of 2-{4-[6-chloro-2-(1-hydroxy-1-methylethyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl acetate (300 mg, 0.68 mmol) in dichloromethane (15 ml) was added thionyl chloride (0.07 ml, 1.02 mmol) and the reaction mixture was refluxed overnight. The reaction mixture was poured into water (10 ml) and the mixture was extracted with dichloromethane (30 ml). The organic layer was washed with brine (10 ml), then dried (Na₂SO₄). The solvent was removed to give 273 mg (87%) of the title compound as white amorphous.

MS (EI) m/z: 458 (M⁺).

STEP 2. 2-{4-[2-(1-azido-1-methylethyl)-6-chloro-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl acetate

A mixture of 2-{4-[6-chloro-2-(1-chloro-1-methylethyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl acetate (step 1, 273 mg, 0.68 mmol), sodium azide (88 mg, 1.36 mmol), KI (112 mg, 0.68 mmol) in DMF (8 ml) was stirred under nitrogen at room temperature for 5.5 h. The reaction mixture was poured into water (5 ml) and the aqueous mixture was extracted with ethyl acetate (30 ml). The organic layer was washed with water (5 ml) and brine (10 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by flash column chromatography eluting with hexane/ethyl acetate (2/1) to afford 133 mg (42%) of the title compound as yellow oil.

MS (EI) m/z: 465 (M^+)

$^1\text{H-NMR}$ (CDCl_3) δ : 8.17 (1H, s), 7.46 (2H, d, $J=8.4$ Hz), 7.35 (2H, d, $J=8.4$ Hz), 7.02 (1H, s), 4.39 (2H, t, $J=7.0$ Hz), 3.09 (2H, t, $J=7.0$ Hz), 2.08 (3H, s), 1.70 (6H, s).

5 STEP 3. 2-{4-[2-(1-amino-1-methylethyl)-6-chloro-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl acetate

A mixture of 2-{4-[2-(1-azido-1-methylethyl)-6-chloro-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl acetate (step 2, 133 mg, 0.28 mmol) and Lindlar catalyst (13 mg) in methanol (5 ml) was stirred under H_2 atmosphere at room temperature for 2.5 h. The catalyst was removed by filtration through a pad of celite and the filtrates were concentrated to give the title compound as yellow oil (121 mg, 98%).

MS (EI) m/z: 439 (M^+)

15 STEP 4. 2-{4-[2-[1-(acetylamino)-1-methylethyl]-6-chloro-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl acetate

To a solution of 2-{4-[2-(1-amino-1-methylethyl)-6-chloro-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl acetate (step 3, 121 mg, 0.27 mmol) in dichloromethane (5 ml) was added acetyl chloride (0.02 ml, 0.3 mmol). The reaction mixture was stirred at room temperature for 7 h. To the reaction mixture was added water (5 ml) and the aqueous mixture was extracted with dichloromethane (30 ml). The organic layer was washed with water (5 ml) and brine (10 ml), then dried (Na_2SO_4). After removal of solvent, the crude product was purified by flash column chromatography eluting with CH_2Cl_2 /methanol (10/1) to afford 76 mg (57%) of the title compound as white amorphous.

25 MS (EI) m/z: 481 (M^+)

¹H-NMR (CDCl₃) δ: 8.14 (1H, s), 7.42 (2H, d, J=8.2 Hz), 7.28 (2H, d, J=8.4 Hz), 6.91 (1H, s), 4.38 (2H, t, J=6.6 Hz), 3.07 (2H, t, J=6.6 Hz), 2.06 (3H, s), 1.75 (6H, s), 1.68 (3H, s).

STEP 5. *N*-{1-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]-1-methylethyl}acetamide

The title compound was prepared according to the procedure described in step 6 of Example 1 2-{4-[2-[1-(acetylamino)-1-methylethyl]-6-chloro-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl acetate(step 4).

¹H-NMR (CDCl₃) δ: 8.13 (1H, s), 7.44 (2H, d, J=8.4 Hz), 7.27 (2H, d, J=8.4 Hz), 6.92 (1H, s), 5.95 (1H, br.s), 3.98 (2H, t, J=6.4 Hz), 2.99 (2H, t, J=6.4 Hz), 1.68-1.75 (9H, m).

STEP 6. 2-{4-[2-[1-(acetylamino)-1-methylethyl]-6-chloro-5-(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate

The title compound was prepared according to the procedure described in

Example 3 from *N*-{1-[6-chloro-1-[4-(2-hydroxyethyl)phenyl]-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]-1-methylethyl}acetamide (step 5).

MS (ESI) *m/z*: 637 (MH⁺), 635 ([M-H]⁻)

¹H-NMR (CD₃OD) δ: 8.04 (1H, s), 7.83 (2H, d, J=8.4 Hz), 7.45 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.5 Hz), 7.26 (2H, d, J=8.5 Hz), 6.93 (1H, s), 4.32 (2H, t, J=6.4 Hz), 3.02 (2H, t, J=6.4 Hz), 2.37 (3H, s), 1.75 (6H, s), 1.53 (3H, s).

EXAMPLE 378

2-{4-[2-[1-(ACETYLAMINO)-1-METHYLETHYL]-6-CHLORO-5-(TRIFLUOROMETHYL)-1*H*-BENZIMIDAZOL-1-YL]PHENYL}ETHYL (4-METHYLPHENYL)SULFONYLCARBAMATE *P*-TOLUENESULFONATE

The title compound was prepared according to the procedure described in Example 231 from *N*-{[(2-{4-[6-chloro-2-[1-(methoxy)ethyl]-5-

(trifluoromethyl)-1*H*-benzimidazol-1-yl]phenyl] ethyl)amino]carbonyl}-4-methylbenzenesulfonamide (Example 377)

IR (KBr) v: 1751, 1508, 1450, 1340, 1161, 1122 cm⁻¹

EXAMPLE 379

5 6-CHLORO-2-ETHYL-1-(4-{2-[METHYL({[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1*H*-BENZIMIDAZOLE-5-CARBOXAMIDE

STEP 1. 2-{4-[5-(aminocarbonyl)-6-chloro-2-ethyl-1*H*-benzimidazol-1-yl]phenyl}ethyl methanesulfonate

10 A mixture of 6-chloro-2-ethyl-1-[4-(2-hydroxyethyl)phenyl]-1*H*-benzimidazole-5-carboxamide (Example 111, step 4, 500 mg, 1.45 mmol), triethylamine (293 mg, 2.90 mmol) and methansulfonyl chloride (322 mg, 2.9 mmol) in dichloromethane (20 ml) was stirred at room temperature for 6 h. The reaction mixture was poured into water, and extracted with dichloromethane (50 ml).

15 The organic layer was washed with brine (50 ml), then dried (Na₂SO₄). After removal of solvent, the crude product was purified by TLC with hexane/ethyl acetate (1:1) to afford 304 mg (50%) of the title compound as white solids.
MS (ESI) m/z: 422 ([M+H]⁺).

¹H-NMR (CDCl₃) δ: 7.54 (1H, s), 7.44 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 7.13 (1H, s), 3.82 (2H, t, J=7.0 Hz), 3.19 (2H, t, J=7.0 Hz), 2.82 (6H, s), 2.75 (2H, q, J=7.6 Hz), 1.35 (3H, t, J=7.6 Hz).

STEP 2. 6-chloro-2-ethyl-1-{4-[2-(methylamino)ethyl]phenyl}-1*H*-benzimidazole-5-carboxamide

A mixture of 2-{4-[5-(aminocarbonyl)-6-chloro-2-ethyl-1*H*-benzimidazol-1-yl]phenyl}ethyl methanesulfonate (step 1, 304 mg, 0.72 mmol), a solution of methyl amine (40% in methanol, 10 ml) and water (5 ml) in a sealed tube was heated overnight at 100 °C. The reaction mixture was partitioned between

09977761.101501

dichloromethane (30 ml) and water (30 ml). The organic phase was separated and the aqueous phase was extracted with dichloromethane (50 ml). The combined organic phases were washed with brine (50 ml) and dried (Na₂SO₄).

After removal of solvent, the crude product was purified by TLC with

- 5 dichloromethane/methanol (10:1) to afford 154 mg (60%) of the title compound as yellow solids.

¹H-NMR (CDCl₃) δ: 7.54 (1H, s), 7.43 (2H, d, J=8.2 Hz), 7.29 (2H, d, J=8.2 Hz), 7.12 (1H, s), 3.62 (2H, t, J=7.0 Hz), 3.01 (2H, t, J=7.0 Hz), 2.82 (6H, s), 2.75 (2H, q, J=7.6 Hz), 1.34 (2H, t, J=7.6 Hz).

- 10 STEP 3. 6-chloro-2-ethyl-1-(4-{2-[methyl({[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1H-benzimidazole-5-carboxamide

The reaction was carried out according to the procedure described in step 10 of Example 1 from 6-chloro-2-ethyl-1-(4-[2-(methylamino)ethyl]phenyl)-1H-

- 15 benzimidazole-5-carboxamide (step2).

MS (ESI) m/z: 554 (MH⁺), 552 ([M-H]⁻).

¹H-NMR (CDCl₃) δ: 8.09 (1H, s), 7.97-7.94 (2H, d, J = 8.4 Hz), 7.40-7.31 (4H, m), 7.16-7.13 (2H, d, J = 8.4 Hz), 7.07 (1H, s), 6.36 (1H, br), 3.52 (2H, br), 2.98 (2H, br), 2.93 (3H, s), 2.78-2.69 (2H, d, J = 7.6 Hz), 2.42 (3H, s), 1.34-1.28 (3H, t, J=7.6 Hz).

- 20 EXAMPLE 380

6-CHLORO-2-ETHYL-1-(4-{2-[METHYL({[(4-METHYLPHENYL)SULFONYL]AMINO}CARBONYL)AMINO]ETHYL}PHENYL)-1H-BENZIMIDAZOLE-5-CARBOXAMIDE SODIUM SALT

- 25 The title compound was prepared according to the procedure described in Example 2 from 6-chloro-2-ethyl-1-(4-{2-[methyl({[(4-

methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl}phenyl)-1*H*-benzimidazole-5-carboxamide (Example 379).
MS (ESI) *m/z*: 554 (MH⁺), 552 ([M-H]⁻).

5 **Screening Methods**

The present invention also features screening assays for the identification of EP4 inhibitors that inhibit EP4 activity at the *in vivo* level.

First, agents are identified which selectively inhibit EP4 activity or selectively bind EP4 over EP1, EP2, and EP3 activity, as determined by functional studies and/or by selective binding studies. Briefly, cells are obtained that predominantly express only one of the EP receptor isoforms. For example, four strains of host cells (e.g., HEK-293 cells) can be genetically engineered to express one of the EP receptors: EP1, EP2, EP3, and EP4. Such cells can be used, in the presence and absence of test agents, for EP receptor functional studies or EP receptor binding studies as reported in the art (see, e.g., Cameron et al., EP 1121939, Fabre et al., J. Clin. Invest. 107: 603-10, 2001, Sakuma et al., J. Bone Miner. Res. 15: 218-27, 2000, and Ungrin et al., Mol. Pharmacol. 59: 1446-56, 2001).

Second, agents identified as selectively inhibiting EP4 activity or selectively binding EP4 are administered to test animals in which rheumatoid arthritis is experimentally induced (e.g., via injection of type II collagen, injection of an anti-type II collagen antibody, or antigen-induced arthritis). Test agents that reduce joint inflammation, joint swelling, joint ankylosis, interleukin (IL)-6, and/or serum amyloid A protein (SAA), and/or increase joint mobility are identified as agents that inhibit EP4 activity at the *in vivo* level.

The test agents used for screening assays of the present invention may be selected individually or obtained from a compound library. Such agents include peptides, combinatorial chemistry-derived molecular libraries made of D- and/or L-configuration amino acids, phosphopeptides, anti-EP4 antibodies,

- 5 EP4 antisense nucleic acids, and small organic and inorganic compounds. Libraries include biological libraries, libraries of natural compounds, peptoid libraries (libraries of molecules having the functions of peptides, but with novel, non-peptide backbones which are resistant to enzymatic degradation yet remain bioactive) (see, e.g., Zuckermann, J. Med. Chem. 37: 2678-85, 10 1994), spatially addressable parallel solid phase or solution phase libraries, synthetic library methods requiring deconvolution, the "one-bead one-compound" library method, and synthetic library methods using affinity chromatography selection.

- 15 Examples of methods for the synthesis of molecular libraries can be found in the art, for example, in DeWitt et al., Proc. Natl. Acad. Sci. 90: 6909, 1993; Erd et al., Proc. Natl. Acad. Sci. 91: 11422, 1994; Zuckermann et al., J. Med. Chem. 37: 2678, 1994; Cho et al., Science, 261: 1303, 1995; Carrell et al., Angew. Chem. Int. Ed. Engl. 33: 2061, 1994; and Gallop et al., J. Med. Chem. 37: 1233, 1994.

- 20 Libraries of compounds may be presented in solution (e.g., Houghten, Biotechniques, 13: 412-421, 1992), or on beads (Lam, Nature 354: 82-84, 1991), on chips (Fodor, Nature 364: 555-556, 1993), bacteria or spores (Ladner, U.S. Patent No. 5,223,409), plasmids (Cull et al., Proc. Natl. Acad. Sci. USA. 89: 1865-1869, 1992) or on phage (Scott et al., Science 249: 386- 25 390, 1990; Devlin, Science 249: 404-406, 1990; Cwirla et al., Proc. Natl. Acad. Sci. (USA) 87: 6378-6382, 1990; Felici, J. Mol. Biol. 222: 301-310, 1991; Ladner, *supra*).